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A CASE OF LATE INFANTILE AMAUROTIC IDIOCY,

WITH PATHOLOGICAL REPORT

BY

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Few degenerative diseases of the nervous system have acquired a wider expansion of their original definition than amaurotic idiocy. Believed in the first place to be limited to Jewish infants (Waren Tay[1], Sachs[2]), it was not long before cases were discovered among Gentiles, in whom also the ocular changes and age of onset were not typical (Batten[3]). During the last fifty years these variations of the disease have appeared under various titles; 'late infantile form' (Jansky[4], Bielschowsky[5]); 'juvenile form' (Vogt[6], Spielmeyer[7], Greenfield and Holmes[8]); and more recently 'late form' (Kufs[9], Meyer[10]). Clinically there may be great differences in these various types; in fact, but for the characteristic histo-pathological changes in all of them, it would be difficult to establish a common identity. The clinical picture of Tay-Sachs' disease in infants, for instance, is quite unrecognizable in Kufs' ex-service man of 42. The marked differences in the appearance of the disease depend on variations in the intensity, extent and special localization of the cell degeneration in the brain. The rate at which the degenerative process proceeds also plays an important part, and in the juvenile and late forms the illness may be prolonged for over ten years (Schönfeld[11], Kufs[9]). Not uncommonly the case remains undiagnosed until a study of the morbid anatomy becomes possible.

Even the name amaurotic family idiocy may finally need modification, since sporadic cases are not uncommon at any age, and amaurosis may be absent or play a secondary part in the juvenile and late forms. Idiocy appears to be the only constant feature. The greatest changes in the clinical picture of the varieties of this disorder make their appearance somewhere between the infantile and juvenile forms. Hence the rare 'late infantile' cases become especially important as a link between the two, for already the hall-mark has become blurred. Racial preponderance is no longer obvious, macular changes are often absent and the course of the disease is more protracted.

These considerations prompt us to publish this 'late infantile' case, particularly as it is the earliest in a Gentile which has been pathologically

recorded. The degree of swellings on the axons in the cortex is probably also unique.

Case report.

Pauline M. first came under observation at the age of 1 year and 10 months. She was the first child of English parents with no history of Jewish intermarriage in the family, and there had been no previous miscarriage. The birth had been normal, with an easy confinement lasting twenty-four hours. Up to the age of 6 months the child appeared to be developing normally. She seemed intelligent, smiled and cried like an ordinary infant, and had already become well trained in the use of the chamber. At 10 months the parents first noticed something amiss when no attempt was made to sit up, and it was not until 14 months that the infant began to lift her head from the pillow. The two other most obvious signs of backwardness were an inability to take solids and very indefinite grasping at objects. Meanwhile the previous cleanliness in habits gradually gave way to incontinence, the child no longer smiled or uttered a cry, but lay still and apathetic in her cot. Short convulsions lasting about a minute commenced at the age of 15 months, two or three daily for three or four days every few weeks. At the same time the child was noticed to jump at any sudden noise.

When first seen spasticity of the arms and legs was already most obvious and the 'toes were pointed.' All the tendon reflexes were much increased, those of the upper extremity less markedly so than the knee and ankle jerks. The abdominal reflexes were absent and the Babinski plantar responses extensor. A loud noise produced a sudden straightening of all the limbs with increased spasticity as in decerebrate rigidity. Gradually the child's general condition deteriorated, the appetite diminished, wasting was rapid, and the fits, which throughout were uninfluenced by luminal and bromide, eventually gave way to complete drowsiness with periodic twitching of the face. The arms were held straight and pronated with the wrists and fingers tightly flexed, while the legs were fixed in a position of moderate talipes equino-varus. The eyes fixed on no object and appeared to be blind; the pupils were half dilated, reacted sluggishly to light, and a varying left external strabismus was present. Both discs showed primary optic atrophy, but there were no macular changes.

The Wassermann reaction of both blood and spinal fluid was negative, and an intradermal Mantoux test provoked no reaction. Further examination showed the cerebro-spinal fluid to be clear and colourless, with less than one cell per c.mm. Sugar was present, globulin absent, and the protein 30 mgm. per c.mm.

The final course of the disease was rapid and the child succumbed to broncho-pneumonia at the age of 1 year and 10 months.

Pathological examination*.

The brain, spinal cord and optic nerve with small portion of retina were removed within twelve hours of death and immediately placed in formol saline.

Dr. Ellison who performed the rest of the post-mortem examination reported patches of broncho-pneumonia. The liver and spleen were carefully examined but showed no changes such as described by Neimann and Pick. Other organs in the body showed no morbid changes of any particular interest.

Histological examination.—Frozen sections of the brain and spinal cord were stained with Scharlach R. and an acid haematoxylin counterstain to demonstrate lipoid deposits in the nerve cells; and histo-chemical tests were performed on frozen sections of the basal ganglia in order to ascertain the nature of these deposits. Anderson's Victoria blue method for neuroglia, and Da Fano's modification of Bielschowsky's method for neurofibrils were also used on frozen sections. Celloidin

* A grant from the Medical Research Council was received in connexion with this part of the investigation.

sections were made from various parts of the brain, spinal cord and optic nerve. These were stained by the Nissl method, by iron haematoxylin with van Gieson's counterstain, by Mallory's phosphotungstic acid method for neuroglia, and by the Weigert-Pal method. The fragment of retina was embedded in paraffin and subsequently cut in serial section.

The essential features of the microscopical examination are conveniently discussed under the headings of the nerve cells, the neuroglia, and the myelin.

THE NERVE CELLS.—The changes in the nerve cells in this case conformed generally to those which have been described previously in the infantile form of amaurotic family idiocy. The nerve cells of the frontal, temporal and occipital cortex, and of the basal ganglia, midbrain, pons, medulla and spinal cord, all presented the rounded, ballooned appearance characteristic of this disease. The cell bodies were swollen and distended by lipoid deposits, the nature of which will be considered later. In the

FIG. 1.—Two pyramidal nerve cells from the occipital cortex with balloon-like swellings on the axons (Bielschowsky stain).

FIG. 2.—Two pyramidal nerve cells with balloon-like swelling on their axons; in one the cell body is also distended with lipoid (Bielschowsky stain).

cortex cerebri many cells showed fusiform or globular swellings on the proximal part of their axon. The most bizarre forms were seen in the occipital cortex (Fig. 1 and 2). Here many of the pyramidal nerve cells appeared normal in size, whilst the swellings on their axons were larger than the cells themselves. The shape of the swellings was variable; globular, ellipitical and fusiform examples were common, and occasionally in the occipital cortex curious kidney-shaped swellings were found.

Among the nerve cells of the frontal cortex there were some smaller cells with a globular, sharply outlined cell body, and a small irregular nucleus resembling that of microglial cells. With Scharlach R. these cells stained rather more brightly than the nerve cells, and with high powers could be seen to be filled with clear yellowish or pale pink globules. Darker staining fatty granules could also be seen in some of them.

The cerebellum was not greatly atrophied, nor was there much shrinkage of the foliae, although they had a more rounded contour and felt firmer than normal.

Histologically the changes here were diffuse rather than intense. The Purkinje cells were not noticeably decreased in number and were surrounded by normal basket fibres. Their cell bodies were considerably swollen with lipoid, and lipoid swellings were seen on their dendrites, usually at the points of branching (Fig. 3). The granule cell layer was considerably atrophied. At least half the granule cells had disappeared, and between those that remained were seen numerous small globular cells filled with yellowish clear pigment, similar to those found in the frontal cortex. There was also, external to the thinned zone of granules and in line with the Purkinje cells, a fairly compact layer, one or two cells thick, of clear, oval nuclei which appeared to give origin to firm neuroglial fibres (Fig. 4). Similar nuclei were seen among the granules and

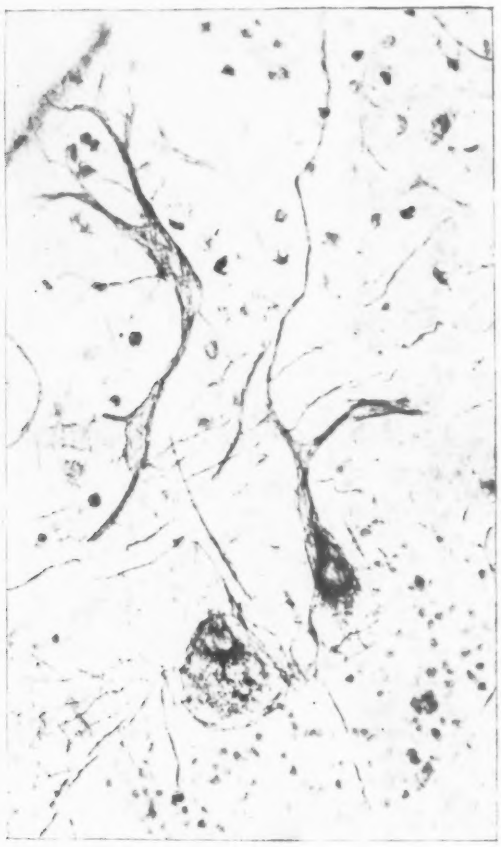

FIG. 3.—Purkinje cells from cerebellar cortex, showing antler-like swellings on their dendrites. In one the axonal end of the cell is also distended with lipoid (Bielschowsky stain).

in the white centre of the foliae. No lipoid could be seen round any of these neuroglial nuclei.

Although the contour of the nerve cells throughout the central nervous system was altered by the deposition of lipoid substances within their cytoplasm, the neurofibrils were singularly unaffected. Bielschowsky preparations showed that the neurofibrils were displaced to the periphery of the body of the affected cell, but that they passed normally into the dendrites and through the swellings.

Histo-chemical investigation of the intracellular lipoid deposits gave the following results:—with Scharlach R. the lipoid gave a bright pink coloration

distinct from that given by neutral fats. Heidenhain's haematoxylin stained the intracellular lipoid deeply. It was not dissolved out by immersing sections for twenty-four hours in absolute alcohol, acetone, chloroform or acid alcohol, but thereafter no coloration, or only a faint pink tinge, was obtained with Scharlach R. It was not doubly refractile.

A comparison between the chemical nature of the intracellular lipoid peculiar to the disease process in amaurotic family idiocy, normal myelin and the neutral fat products of degeneration resulting from disintegration of myelin, was possible by

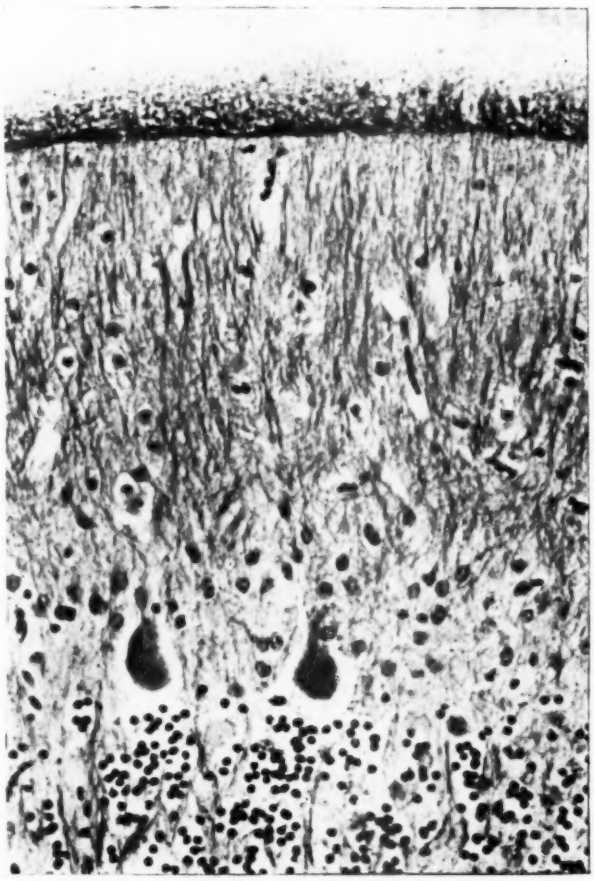

FIG. 4.—Cerebellar cortex, stained by Mallory's neuroglia stain, and showing a great overgrowth of neuroglia throughout the cortex, especially in the subpial layer.

a study of Kultschitsky-Pal preparations through the basal ganglia. Widespread degeneration of myelinated fibres in the internal capsule had taken place, and in both the anterior and posterior limbs of the capsule were to be seen a large number of compound granular corpuscles loaded with fat granules. The effect of mordanting frozen sections for different lengths of time in Weigert's mordant and subsequently staining them with Kultschitsky's haematoxylin, as recommended by Hurst[12], was to demonstrate that the intracellular lipoid in the case under consideration occupied a position in the fatty series, according to Hurst's classification, mid-way between the composition of normal myelin and the neutral fats. After twenty-four hours in mordant normal myelin stained fairly well with haematoxylin; neither the lipoid granules nor the products of myelin degeneration stained at all. Normal myelin stained best after

forty-eight hours in mordant, at a time when the degeneration products did not stain at all, though the intracellular lipoid stained well. Optimum staining of the intracellular lipoid was obtained by mordanting for four days. The degeneration products of myelin also stained well when mordanted for the same length of time, whereas normal myelin gave only a faint blue coloration. The intracellular lipoid was recognizable at the end of a week in mordant, when no appreciable staining of normal myelin could be obtained. The neutral fat in the compound granular corpuscles and in the degenerated fibres stained well after this period of mordanting. These results indicated that the intracellular lipoid consisted of a compound of phosphatides and cerebrosides, which, in its reactions, was intermediate between normal myelin and neutral fat.

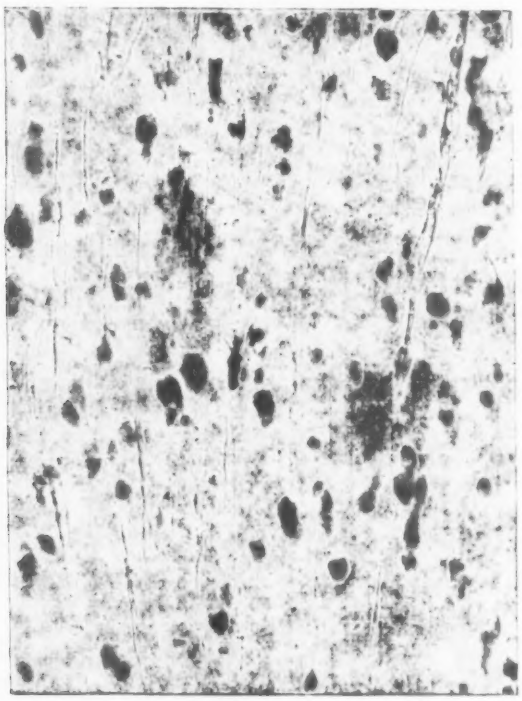

FIG. 5.—Frontal cortex stained by Weigert-Pal method. The lipoid swellings stain along with the radial fibres.

NEUROGLIA.—The sub-pial neuroglia in the cerebral cortex had greatly proliferated, producing a dense gliosis of the superficial layers of the cortex. This was especially well seen in the occipital region, where there was a thick down-growth of neuroglia into the third layer of the cortex. Peri-ventricular gliosis was also striking, especially in the fourth ventricle. Other regions of the brain showed a remarkable gliosis; in the cerebellum there was considerable gliosis of the molecular layer, especially just under the surface, where a thick feltwork of neuroglial fibres was to be seen in preparations stained with Victoria blue or phosphotungstic acid haematoxylin (Fig. 4). In the thalamus, which had felt unduly firm macroscopically, a very severe gliosis was found, perhaps more intense in the medial than in the lateral part. The lenticular and caudate nuclei were relatively unaffected, though some proliferation of neuroglia had occurred in them also.

MYELIN.—The fibres in the cerebral cortex were, in general, well myelinated, though in the frontal region some of the more superficial tangential fibres stained

poorly. In the internal capsule, the fibres in the anterior two-thirds of the anterior limb of the capsule had undergone almost complete degeneration. In the genu there were many finely myelinated fibres, but in the posterior limb, with the exception of a few finely myelinated fibres in its most anterior part, all the fibres

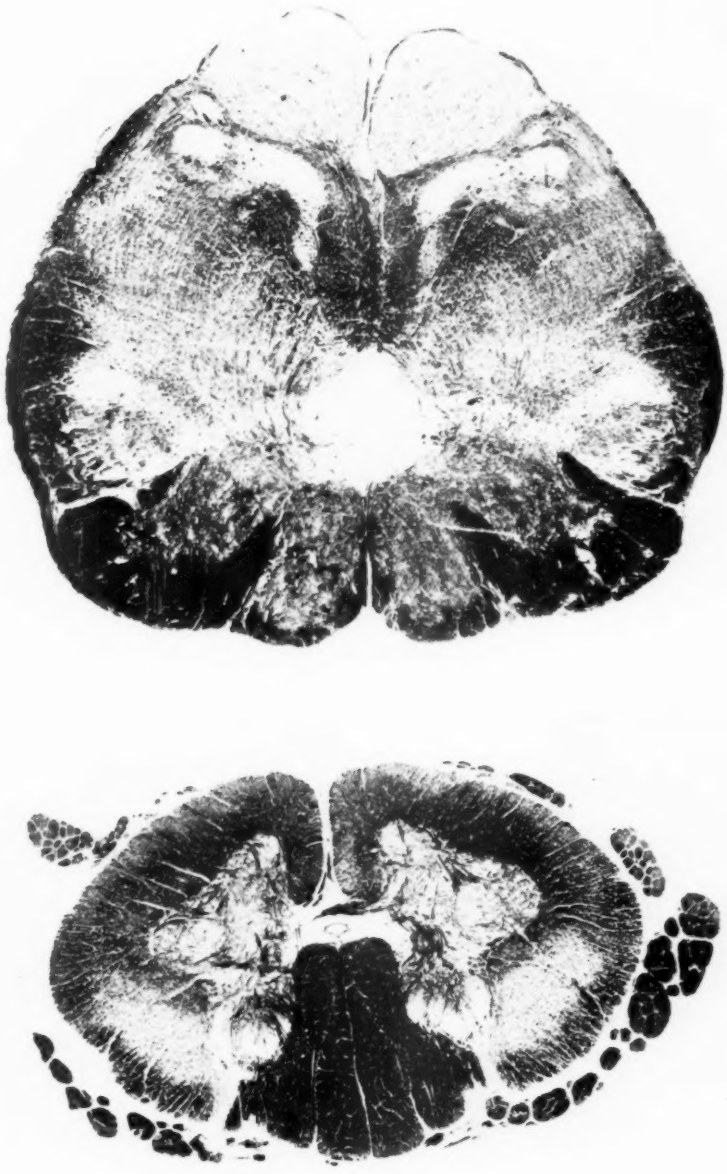

FIG. 6 & 7.—Transverse sections of medulla and cervical cord, stained by the Weigert-Pal method to show the degeneration of the pyramidal tracts.

had degenerated. The outer parts of the crura were unaffected, but the medial and fronto-pontine fibres were degenerated. In the medulla there was almost complete destruction of the pyramids, and the pyramidal tracts were degenerated throughout the spinal cord.

Optic nerve and retina.—In longitudinal sections of the optic nerve many poorly myelinated fibres were seen, and in addition there were many fibres in an early stage of degeneration. There was no neuroglial reaction to this degeneration.

It was not possible to decide whether the appearance of the retina was pathological or not, owing to the conditions of its fixation. The only definite opinion that could be given on the fragment sectioned was regarding the number of ganglion cells; these were considerably fewer in number than those seen in sections of a normal retina. Those present appeared healthy.

Summary.—1. The nerve cells throughout the central nervous system presented the swollen, ballooned appearance characteristic of amaurotic family idiocy.

2. This swelling of the nerve cells was due to distension by deposition in them of a lipoid substance. Histo-chemical tests showed this to be a compound of cerebrosides and phosphatides, occupying an intermediate position chemically between normal myelin and neutral fat.

3. Similar swellings were found on many axons of nerve cells; in some situations, notably in the frontal and occipital cortex, these axonal swellings were larger than the cells themselves.

4. Intense gliosis was present in the superficial layers of the cerebral cortex and of the cerebellum; also in the optic thalamus and round the ventricles.

5. There was degeneration of the fronto-pontine and of the pyramidal fibres, and of some fibres of the optic nerve.

6. There was a loss of ganglion cells in the retina.

Discussion.

The view of both Pick and Bielschowsky[13] is that all forms of familial amaurotic idiocy are due to a disturbance of lipoid metabolism, and Marinesco's[14] work goes a long way towards establishing this. The same primary disturbance of lipoid metabolism is present in certain cases of Niemann-Pick disease, and it is now generally held that the two conditions are related by more than a chance association, and that, in fact, they are different manifestations of the same disease process. That cases of amaurotic idiocy do occur with no lipoid changes in the liver and spleen, and vice versa, is no reason to doubt this.

The alteration in the cells of the liver and spleen in Niemann-Pick disease is mainly due to a deposition of phosphatid molecules. In amaurotic idiocy we have shown, as others have done, that the lipoid deposit causing distension of the cells of the brain is also largely composed of phosphatid. The fundamental cause of this disturbance of lipoid metabolism, however, still remains unknown.

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INVESTIGATIONS ON GLYCOGEN DISEASE

BY

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Under the title ' chronic hepatogenic hypoglycaemia in childhood ' we described[1, 2] some time ago a number of investigations in a boy who had had a very large liver since birth. Clinically he gave the impression of adiposogenital dystrophy, and, in addition, he showed a very marked disturbance of carbohydrate metabolism. The predominant features of this disturbance were chronic hypoglycaemia in the fasting state, without the usual symptoms, and accompanied by ketosis; little or no change in the blood-sugar value after subcutaneous injection of adrenalin, and hypersensitiveness to small quantities of insulin. As a cause of this anomalous disturbance we conceived a continuation of the foetal condition, and we sought in faulty glycogenolysis an explanation of the condition. Thus in our boy the ketosis and the absence of hyperglycaemic response to adrenalin might not depend upon a poor glycogen content of the liver.

We found support for our ideas especially in the publications of von Gierke[3, 4] and Schönheimer[5]. We thought we had to deal in our boy with a case of hepatomegalia glycogenica as described by von Gierke, and that the disturbances in metabolism in our case were characteristic for this form of liver hypertrophy. The features of this hypertrophy were the accumulation of glycogen, which during life and after death could be mobilized only with difficulty. Since then the interest in ' glycogen disease ' has greatly increased and different authors[6-12a] have published definite cases of ' hepatomegalia glycogenica,' which have been studied clinically. The deviations in metabolism found by these authors as a whole agree with those found in our case. In our opinion our case is therefore one of hepatomegalia glycogenica and in this we are supported by the recent findings of other investigators. It is important to note that this interesting glycogen disease must be regarded as a general disease of metabolism, in which the glycogen can only be mobilized with difficulty, and may accumulate in various organs, not only in the liver. In this way it may give rise to hypertrophy of different organs. This accumulation of glycogen plays a big rôle in the occurrence of a number of congenital deviations and in those arising shortly after birth. Thus, it is a disturbance which merits the consideration of paediatricians, and the study of this disturbance will increase our insight into several diseases of childhood. Further, glycogen disease and

the conduct of the glycogen in this disease have undoubtedly a very interesting and more general physiological and pathological significance. Elsewhere[13, 14] we have written more extensively upon the significance of glycogen in the occurrence of hypertrophy of other organs than the liver (heart, kidneys, pylorus).

We have been able to continue our observations in this patient with the large liver and to extend our researches during last year. Further, a second child, which presented almost the same morbid picture with analogous deviations in metabolism, has come under our care. We have attempted, as before, to investigate the disturbance of metabolism in this disease, and to make more exact its differential diagnosis from other chronic liver diseases, especially from the cirrhoses.

B., a girl, the second case, now six years old, was a full-term child, delivered spontaneously. Throughout her pregnancy the mother remained well. The child's weight at birth was just over 7 lb. She was breast-fed until the age of 10 months. Her weight when one year old was about 21 lb. Throughout this time the physical condition remained good and there was no evidence of rickets. The mental development of the child was normal. Though not clinically established there is much evidence to suggest that the child at birth had already a large liver. In a photograph, taken at the age of 6 months, the abnormally large circumference of the abdomen can be distinctly seen, and before the end of the first year the presence of an abnormally large liver had been established with certainty. We know that during the first year of life no peculiarities occurred.

After the first year of life this child, just as in the case of our first patient, had periodic attacks of persistent vomiting in the morning and showed also a special preference for bread. When the mother came to us with the child in January, 1932, there were no other complaints apart from this nausea and vomiting. The child was hindered in her movements by the enormous abdomen. The child was alert. The mental development was normal and she went to a preparatory school. She had a good appetite, preferred bread, had no complaints of the abdomen, and no attacks of fever.

Father normal. Mother was 37 years when the child was born, this being her 7th pregnancy and the first child of her second marriage. She had had one abortion, once a still-born twin; one child died at the age of one year from broncho-pneumonia following measles. The other children are normal; no known enlargement of the liver in the family. Of the medical condition of the first husband little is known, except that he was a drunkard. The Wassermann reaction (Jan., 1932) in the mother was negative. Since the birth of the girl the mother has had no further pregnancies. No family history of tuberculosis.

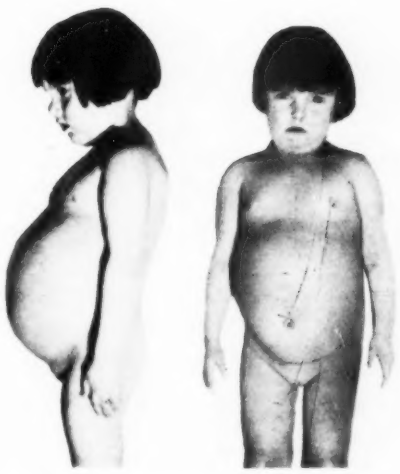
On examination (Jan., 1932) the girl, nearly 5 years old, weighed 35½ lb., and was only 38 in. in height. She was well nourished with normal subcutaneous fat, and no suggestion of adiposity. No icterus. Colour of the skin was somewhat dark but showed no pigmentation of skin or mucous membranes. No abnormal growth of hair. Rather marked dental caries. The neck was short, and on both sides were numerous small glands. The abdomen was protuberant. Heart, blood-pressure and lungs were normal.

The abdomen was greatly distended as a whole, and on the upper part of the wall of the abdomen a fine net of veins was seen; no caput medusae. The distension of the abdomen was caused by a very large liver, which occupied nearly the whole right and the greater part of the left half of the abdomen. On the right side it was almost impossible to place the hand between the liver and the edge of the pelvis. The left lobe of the liver could be felt from the level of the umbilicus, slanting upwards and disappearing under the costal arch at about the axillary line. Just at the umbilicus an incisura could be felt. The liver was of firm consistence and felt smooth; its

edge was sharp. No pain on palpation of the abdomen. No signs of free fluid. The greatest circumference of the chest was 21 in. and of the abdomen 25 in. The spleen could with difficulty be felt; kidneys not palpable. External genitals normal. Reflexes normal, muscular system normal; the legs slim. The child was not easily exhausted by exercise.

The child was intellectually normal. She complained of no abdominal symptoms, and showed no clubbing of the fingers.

The urine in fasting condition contained no albumen or sugar, and showed a weakly positive reaction for urobilin, and strongly positive tests for acetone and diacetic acid. Bile absent. Specific gravity normal. Nothing abnormal in the sediment. Stool: normal colour and consistency; no worms or ova; on a mixed diet the fat-content was not increased. The Pirquet, Wassermann and Weinberg reactions were all negative. Temperature normal.



Examination of the blood showed a leucocyte count of 12,700 with 5 per cent. eosinophils and a moderate relative lymphocytosis; no anaemia; platelets normal. Throughout the last year the blood was investigated repeatedly with similar results; except that the leucocyte count was normal and the eosinophilia less. A distinct leucopenia, as found in the boy, was not found.

X-ray investigation: no enlargement of the heart; no signs of active rickets; no apparent abnormalities of the extremities with the exception of several small transverse lines in the bones of the lower extremities as a sign of irregular growth; some delayed ossification, in both wrists only three of the small bones were ossified. Sella turcica normal. Kidneys normal; no abnormalities in the region of the adrenal glands. Bones of the skull were normal.

Electrocardiogram normal. Basal metabolism slightly increased (two determinations, +19 and +27 per cent. At the second determination the child was not quiet).

The girl therefore showed a greatly enlarged liver without demonstrable hypertrophy of other organs, but with definitely delayed growth. Marked ketosis and slight urobilinuria were present. No signs of an endocrine disturbance were found and especially no marked adiposity as was found in our boy.

Blood sugar.—In the fasting condition there was a combination of hypoglycaemia and ketosis: in the capillary blood the blood sugar at different determinations ranged between 0·046 and 0·059 per cent.; in the venous blood between 0·05 and 0·06 per cent. (Hagedorn and Jensen).

In our boy the fasting blood-sugar values now show a tendency to rise (in the capillary blood 0·057–0·073 per cent.). In the girl all clinical symptoms of the so-called hypoglycaemic complex as occurs in hyper-insulinism were absent.

In addition, after 25 gm. of glucose the girl showed a biphasic blood-sugar curve. The blood sugar remained increased for a long time and had not returned to the fasting level after 2½ hours, which in itself is strongly against hyper-insulinism. The maximal elevation was only from 0·058 to 0·112 per cent.; no glucosuria occurred.

After 20 gm. of fructose the fasting blood sugar rose from 0·056 to a maximum of 0·088 per cent., i.e., a little higher than may occur normally (30 mgm. per cent.), but the increase lasted for more than two hours. The urine contained no reducing substances, and the ketosis existing in the fasting condition decreased very much after giving fructose.

After 25 gm. of galactose no sugar was excreted in the urine.

The elevation of the respiratory quotient after giving 20 gm. of glucose was investigated; in one hour the quotient rose above 1, but the girl had not remained quiet.

Adrenalin test.—After subcutaneous injection of 0·5 mgm. of adrenalin the girl showed only a very slight elevation of the blood sugar: in the first test from 0·054 to 0·07 per cent., in the second test from 0·051 to 0·066 per cent. But a markedly increased excretion of ketones after the adrenalin injection was noticed. In our boy, although his fasting blood sugar is distinctly higher than formerly, a significant rise of blood sugar after injection of adrenalin does not take place: in one test recently performed a rise from 0·069 to 0·072 per cent. occurred within two hours after the injection.

In view of the adrenalin effect our idea of the cause of the blood-sugar elevation after adrenalin injection must be reconsidered. The Coris[15] have demonstrated in different ways that the blood-sugar elevation which normally occurs after adrenalin injection, is only partly caused by mobilization of liver glycogen and this only in so far as the primary elevation is concerned. In speculating as to the existence of a glycogen depot in the liver which can be mobilized, stress must therefore, a priori, be laid upon the non-appearance of this initial elevation.

In both our patients, however, it appeared that the adrenalin effect was also abnormal in so far as the rise of the lactic acid content of the blood, which normally accompanies adrenalin hyperglycaemia and which is related to an increased splitting of muscle glycogen, was only very small.

In this connection we wish to point out the disturbance of glycogen splitting and of lactic acid formation in muscle, which occurs after extirpation of the adrenals and is accompanied by an increased consumption of creatine phosphoric acid. It appeared that creatine was present in the urine of both our children, but in an amount normal for their age.

In still another way the adrenalin effect in both our children appeared to be deviating from normal. When in normal men subcutaneous injection of adrenalin is combined with oral administration of glucose in an amount normally used for tolerance tests, then the elevation of the blood sugar is for the most part much more marked than after adrenalin injection or glucose ingestion alone (Burkens). This is apparently a consequence of the second adrenalin effect, that is, a decrease of sugar consumption in the muscles by which the extra glucose given orally causes a higher elevation of the blood sugar. In both our patients such a test has been done once. In both cases the elevation of the blood sugar after adrenalin injection together with glucose ingestion, was only slightly greater than after glucose ingestion alone.

From investigation of the protein spectrum of the blood serum it appeared that the very important increase of the globulin content of the serum which is present in the majority of chronic parenchymatous liver affections[16] was absent in both our patients (compare the two control cases in Table 1).

TABLE 1.

PROTEIN SPECTRUM OF BLOOD PLASMA.

(Percentage figures)

	Normal	Glycogen liver		Hepatic cirrh. 12 years	Gaucher's dis. 13 years
		Pat. B.	Pat. E.		
Total protein..	6·5 – 8	8·34	7·63 ..	9·02	91·4
Albumen ..	4·5 – 5·5	5·26	4·66 5·02	4·2	4·11
Globulin ..	1·8 – 2·4	2·69	2·52 2·09	4·28	4·8
Fibrinogen ..	0·25 – 0·38	0·39	0·45 ..	0·54	0·24

Next with the serum of both patients we performed the flocculation test which according to modern investigations is always positive in chronic parenchymatous liver affections (the so-called Takata-Ara reaction)[17]. In our boy E. the test was negative, in the girl B. it was only weakly positive.

Corresponding to the protein spectrum of the serum the sedimentation-rate of the erythrocytes of both our patients in the defibrinated blood as well as in the non-defibrinated blood was normal.

Certain determinations of different constituents of blood and blood serum have also been made in both our patients. Table 2 gives a survey of the results. From this it appears that in the girl as well as in the boy there was a marked elevation of the cholesterol content. In both our patients the relation between free cholesterol and cholesterol esters, a relation which in liver diseases is often changed, was normal. There was no decrease of cholesterol esters. In both our patients with hypoglycaemia the non-sugar reducing fraction and glutathion content (Groen) were normal. It further appeared that the lipolytic activity of the serum of both our patients was

also normal. In addition, a chinine-, and an atoxyl-resistant lipase (as may be present in the serum in parenchymatous liver and pancreas affections) were absent from the serum.

TABLE 2.

SOME CONSTITUENTS OF BLOOD SERUM.

	Pat. E. Per cent.	Pat. B. Per cent.	Normal Per cent.
Cl in total blood	0·29	0·294	0·27– 0·30
Cl in serum	0·38	0·37	0·35– 0·40
Ca in serum	12·56 mgm.	10·70 mgm.	7·8 –11·95 mgm.
Ca in serum ultrafiltrates ..	8·376 mgm.	—	4.86– 6.41 mgm.
Mg in serum...	2·503 mgm.	—	1·5 – 3 mgm.
Mg in serum ultra filtrates ..	1·695 mgm.	—	2 mgm.
Inorganic P in blood ..	4–5 mgm.	3·8 mgm.	2·5 – 4 mgm.
Cholesterol in blood	200–263 mgm.	210–221 mgm.	160 –180 mgm.
Cholesterol in serum	286–333 mgm.	206–294 mgm.	180 –200 mgm.
Free cholesterol	35·5	41	30 –40
Cholesterol esters	64·5	59	60 –70
Non-sugar reducing fraction ..	27·5 mg.m	28 mgm.	22 –28 mgm.
Glutathion	34 mgm.	34 mgm.	25 –40 mgm.
Bilirubin	—	1·08 units	—

GLYCOGEN METABOLISM.—During the last year we studied in different ways the glycogen metabolism of both our patients; firstly, the so-called initial insulin hyperglycaemia which when present would prove the existence of a glycogen depot. The effect is not given by pure insulin preparations[18]. Using an insulin preparation of Burroughs Wellcome & Co., which in animal experiments was proved to produce an initial rise in blood sugar, we found no such effect in our girl (Table 3). The absence of this effect in

TABLE 3.

INVESTIGATION AFTER THE SO-CALLED INSULIN HYPERGLYCAEMIA.

	Blood sugar in mgm. per cent.						Maximal elevation per cent.
	Before	After 5	10	15	20	25	30 Minutes
Normal	91	99	111	101	79	75	... 21·9
Patient B....	58	51	48	37	...	42	... ...
Liver cirrhosis	93	93	86	74	54	54	43 0
Severe jaundice	92	92	88	81	72	63	50 0
Recovered jaundice	79	97	88	68	47	41	47 22·7

her case is, as we now know, not due to an insufficient glycogen depot, but to a glycogen supply which can be mobilised only with difficulty.

The glycolysis of the blood of the girl B. was normal, as was that of the boy E. The same holds true for the influence exerted by insulin in vitro on the oxidative glucose fermentation by erythrocytes[19] of our patients. For this investigation we made use of a pure insulin preparation kindly provided by Prof. Laqueur.

The quantity of diastase in blood and urine of both patients proved to be normal. An increased diastase excretion in the urine, as found by some investigators, was not found by us. Again, the so-called diastase-fortifying action of the blood serum[20], by which is meant the smallest quantity of serum which in vitro exercises a fortifying action on a pancreatic amylase, was normal in both our patients.

Special attention was paid to the glycogen in the blood of our patients. Could this glycogen be split? Little is known up to the present regarding the glycogen of the blood. According to Gabbe[21], in the normal blood the glycogen should, even on keeping for several hours at 37° C., decrease only very slightly, notwithstanding the presence of a glycogenolytic ferment. Thus the blood glycogen should in this stability resemble the glycogen present during foetal life, and differ in this respect from that present in liver and muscle, corresponding to that existing in liver and different organs in glycogen disease.

With our method, which could be regarded as a micro-modification of Pflüger's method, we had obtained for the glycogen content of the blood of the boy E. some results which could be called distinctly high. Since then we have paid special attention to the method of determination of blood glycogen and we have elaborated a method which certainly will be of importance in the future. Our method is as follows:—

Determination of glycogen in 1 c.c. of blood.—1 c.c. of blood is haemolysed by adding 1 c.c. of distilled water in a wide Pyrex centrifuge tube with a ground glass stopper. Two cubic centimetres of 60 per cent. KOH are added and the closed tube is heated in a boiling water bath for 15-20 minutes and carefully shaken from time to time. After cooling, 8 c.c. of distilled water and 16 c.c. of absolute alcohol or 96 per cent. alcohol are added and the contents of the tube carefully mixed. The precipitated glycogen is allowed to settle overnight. After centrifuging, the precipitate is washed at least twice with 66 per cent. alcohol. The glycogen is determinated as glucose by hydrolysing with 4 c.c. 2·2 per cent. HCl for two hours, after evaporation of the remaining alcohol. The material is now neutralised with 2N. NaOH using phenol red (one drop) as indicator. The glucose is determined after the method of Hagedorn and Jensen. The whole determination is thus carried out in the same tube.

In our earlier investigations we did not haemolyse the blood and this is probably the reason why our double determinations did not always correspond. The change in the time of boiling with KOH from two hours to 15-20 minutes we obtained from the recent publication of Good, Kramer and Somogyi[22]. For the rest we still follow the method described above with excellent results; the method was tested using blood to which known amounts of glycogen had been added. We found a maximum error of 10 per cent.

Since we have used the above method for the determination of glycogen we have constantly found in the fasting blood of both our patients values which we look upon as high, no leucocytosis being present which could cause

this elevation. The results of a series of determinations during the past 14 months were as follws:—Glycogen content of blood (as mgm. glucose per 100 c.c. of blood): Patient B. 23·75, 23, 20, 19·25, 21·25, 18·75, 21·35, 21, mean value, 21·04; Patient E. 26, 25, 23·05, 27·5, 22·9, 26·62, 26·25, 24, 28, 25, mean value, 25·43. Next (Table 4) we give the results obtained in a

TABLE 4.

GLYCOGEN CONTENT OF THE BLOOD.

(expressed as glucose in mgm. per cent.)

35 determinations in children:

8 showed	5-10
14 ,,	10-15
10 ,,	15-17
2 ,,	17-20
1 ,,	20-22

Blood from umbilical cord:
13 determinations:

4 showed	5-10
7 ,,	10-15
2 ,,	15-17

Examples	
Cong. pyloric stenosis ...	10·2
	13
Premature infants	13·17
	16·6
	21·25
Hypertrophy of the heart in patent interventricular septum	15·75
	10
Cyclic vomiting	16
	13·38
Microcephaly	18·75
Coeliac disease	12

Determinations in adults:

Addison's disease ...	7·06	Myelogenous leukaemia	71
	7·38	(150,000 white cells)	48·5
Lues hepatis ...	12·12	Renal rickets ...	6·35
Cirrhosis hepatis ...	12·62	Insulin-resistant diabetes	13·3
	17·4		
Congested liver ...	16·75		
	26·1		
Pregnancy	18		
Cholelithiasis ...	12·45		

number of children some of whom were healthy, the others suffering from varying diseases; a number of determinations also were made in blood from the umbilical cord and are noted in this table. In children under 12 years of age, as is reported in the table, with the exception of our patients, we found by our method only one glycogen value above 20 mgm. per cent., and that in a premature child; as a rule the value was much lower. We also once found a value above 20 mgm. per cent. in a child with miliary tuberculosis. On these grounds we think we are justified provisionally in saying that the elevation of the glycogen content of the blood is of some diagnostic significance in the diagnosis of hepatomegalia glycogenica. We say 'provisionally' because blood of infants with other forms of liver

hypertrophy was not available. We were able to examine the blood of adults with marked liver hypertrophy. A priori we are not justified in comparing these values with those obtained in children with liver hypertrophy and especially with those obtained in our patients, because the glycogen metabolism in childhood occupies a separate place, as has been shown clinically and experimentally. In adults with liver hypertrophy values as found in our children also occur. When the number of leucocytes is greatly increased, this in itself may be the explanation of a marked elevation of the glycogen content. In an adult female patient with myeloid leukaemia and a large liver (150,000 leucocytes) we found a very high glycogen content of the blood in two determinations, 48·5 and 71 mgm. per cent., expressed as glucose.

Incidentally it may be noticed that according to the table the glycogen increase did not occur in two cases of pyloric spasm, an affection in which an accumulation of glycogen must be considered as a possible cause of the hypertrophy. Further, we recently found in the case of a baby where at the autopsy histological and histo-chemical, and later on chemical investigation revealed an accumulation of glycogen in the heart muscle (idiopathic hypertrophy of the heart, vide infra), that the blood obtained after death contained 18 mgm. per cent. of glycogen· a value which in our experience is at the highest limit of the normal values. The fluid with which the organs were bathed at autopsy contained however already 87 mgm. per cent. of glycogen. It is improbable that cases of glycogen disease, where hypertrophy does not primarily concern the liver, should show analogous deviations in metabolism to our patients. Little can at present time be said about the glycogen of the blood in such cases.

In Table 4 we give some results obtained in adults suffering from diseases in which the carbohydrate metabolism was specially concerned.

As to the splitting of the glycogen of the blood we agree with Gabbe in judging that this glycogen can be split only with difficulty. Blood was collected with aseptic precaution and received in sterile tubes. After incubation for $1\frac{1}{2}$ hours at 37° C. the blood of our patients showed no splitting of its glycogen. In normal children the blood glycogen not uncommonly shows marked splitting in the same time. In keeping this normal blood for 48 hours at 37° C. we constantly found that a definite but varying decrease of the glycogen content could be demonstrated and in this we differ from Gabbe. In our patients the decrease of the glycogen content of the blood under the same conditions which are so favourable for splitting, proved to be smaller than the mean decrease in the control patients and it scarcely agreed with the lowest values found in control children (Table 5).

Further, we found that glycogen added to serum of our patients and to serum of control patients was split by both in the same degree and in the same time.

Our next step was to find out whether by mixing the blood of our patients with that of control children and keeping it for 48 hours at 37° C.

the splitting of the blood glycogen of our patients could be accelerated. Increased glycogenolysis was not constantly found, however, so that provisionally we are not justified in concluding, as we thought at first, that

TABLE 5.

GLYCOGEN VALUES OF BLOOD DETERMINED DIRECTLY AND AFTER INCUBATION FOR 48 HOURS AT 37° C. EXPRESSED IN MGM. GLUCOSE PER 100 C.C. OF BLOOD.

Control patients	Immediate	After 48 hours at 37° C.	Decrease in per cent.
1	15·75	10·5	33·33
2	13·75	10·25	25·46
3	16·75	9·6	42·68
4	17·4	12·8	26·43
5	15·75	6·5	58·73
6	11·75	5·5	53·2
7	10	5·5	45
8	15·62	7·375	52·79
9	12·12	8	34
10	18	13·75	23·6
11	12·62	8	36·6
			mean decr. 39·26
Patient E			
1	24	19·25	20
2	28	24·25	13·4
3	25	19	24
			mean decr. 19·1
Patient B			
1	21·25	16·5	22·25
2	23·1	18·75	19
			maen decr. 20·62

there exists in normal blood a substance which favours the splitting of the blood glycogen of our patients.

In summarizing (Table 6) the above results of the clinico-chemical investigation, we found in both cases, in addition to our former findings in our boy:—

1. A combination of hypoglycaemia and ketosis in the fasting condition.
2. An abnormal adrenalin effect, expressing itself by:—
   a. Absence of a distinct elevation of the blood sugar.
   b. A marked increase of the ketosis.
   c. Only a small elevation of the lactic acid content of the blood.
3. An abnormal blood sugar curve after ingestion of glucose, unaccompanied by glycosuria.
4. No diminution in tolerance to galactose and fructose.
5. Absence of the so-called initial insulin hyperglycaemia.
6. a. Normal values for the diastase activity of blood and urine.
   b. Normal diastase activating effect of the serum.

7. Increased glycogen content of the blood, which could not be explained by leucocytosis.
8. Normal glycogen splitting activity of the blood serum.
9. Decreased glycogenolysis of the blood glycogen on incubation for two days at 37° C., compared with control cases.
10. Normal protein spectrum, especially no increase of the globulin content.
11. Hypercholesterolaemia with normal relation between free cholesterol and cholesterol esters.

TABLE 6.

SURVEY OF THE MOST IMPORTANT SYMPTOMS IN TWO CASES OF GLYCOGEN LIVER.

Symptoms.	Pat. E.	Pat. B.
Hepatomegalia	+	+
Infantilism	+	+
Adiposity	+	+
Psychical development	normal	normal
Appearance of endocrine disturbance	+	—
Hypoglycaemia plus ketosis	+	+
Blood sugar curve after glucose	abnormal	abnormal
Adrenalin effect blood sugar	„	„
„ „ lactic acid	„	„
Insulin effect, so-called insulin hyperglycaemia		absent
Sensitivity to insulin	+	
Galactose test	normal	normal
Fructose test	„	„
Glycolysis of blood	„	„
Glycogen of blood	increased	increased
Glycogen of serum ultrafiltrate	normal	normal
Glycogenolysis of blood glycogen	decreased	decreased
Splitting of glycogen added to serum	normal	normal
Diastatic power of blood	„	„
„ „ urine	„	„
Water metabolism	disturbed	disturbed
Cholesterol of blood	increased	increased
Proportion of free cholesterol to esters	normal	normal
Protein spectrum of serum	„	„
Urobilinuria	—	+
Basal metabolism	slightly increased	slightly increased
Heart (size, E.C.G.)	normal	normal
Kidney (size)	„	„

We did not think we were justified when we know already so much about the metabolism of our children, in doing a laparotomy and biopsy of the liver in the girl B., as has been done elsewhere (Beumer and Loeschke[6], Schall[8]). In epithelial cells (mucous membrane of the cheek, cells of the mucous membrane of the kidney in the sediment of freshly voided urine) we could demonstrate no glycogen in the girl B. by the staining method of Best. Nor could we find an increased amount of glycogen in the urine. In the leucocytes from a small granuloma at the root of a molar we found much glycogen (de Vries). This in itself certainly has no great significance, but the absence of glycogen in this tissue would not have been in keeping with the morbid picture.

Discussion.

About the cause of the difficulty in the splitting of the glycogen in glycogen disease nothing can be said with certainty. Blood and urine of our patients showed a normal diastatic activity (according to some investigators the urine sometimes showed an increased activity); the diastase in the liver is probably in normal quantity[23]. How is the glycogen in such a particular way protected in this disease? Does it form a compound with protein or have we to deal here with another modification of glycogen without the question of another chemical polysaccharide? Or must we seek the solution in the hormonal direction?

The conception of a glycogen which, for example, was difficult to split owing to an abnormal binding of protein (a conception mentioned by Unshelm), has been investigated by us with the help of W. M. Bendien. We determined the glycogen content of the blood serum of our patients and of that of some control children and then of the ultrafiltrate of these blood sera prepared in different ways. It now appeared that a part of the serum glycogen is always present in the protein-free ultrafiltrate. The values obtained for this ultrafiltrable part of the serum glycogen varied between $2\frac{1}{2}$ and 4 mgm. per cent., with very different values for the serum glycogen. In both our patients the quantity of this ultrafiltrable part showed no departure from normal. When the protein content of the ultrafiltrate was increased[24], the corresponding glycogen content also increased and approximately in proportion to the protein content. We are still investigating whether the non-ultrafiltrable glycogen in the serum is indeed bound to the protein, and whether there are still further differences in this connection between these patients and other normal children. Up to the present we have found no evidence for the existence of a particular combination of the glycogen in our patients.

As to the conception of the glycogen disease as a hormonal disturbance we would note the following. The whole picture of glycogen disease, whether the liver alone is concerned, or whether in addition to this there exists hypertrophy of other organs, cannot be correlated with any known disturbance of internal secretion. We have been able to exclude a hyperinsulinism for different reasons. Also pathological examination of children who showed some hypertrophy of organs by accumulation of glycogen, did not give absolute indications in this respect. Perhaps an exception is provided by the first case of von Gierke, where atrophic adrenals were found, and perhaps also by the patient lately described by Bellingham Smith and O'Flynn[10], who showed marked pigmentation and abnormal growth of hair.

On the other hand, our conceptions about glycogen splitting in liver and muscles have undergone some fundamental changes by recent investigations. Firstly it appears that there exists a nervous influence on liver glycogen, which can express itself otherwise than through adrenalin and insulin. On the basis of these findings MacLeod[25] even speculated as to the existence of two forms of glycogen in the liver, having a different functional behaviour. Further, we must point to the results of recent researches on the influence of the hormone of the adrenal cortex and of the anterior lobe of the pituitary upon carbohydrate metabolism[26].

The essentials of glycogen disease cannot up to the present be wholly explained by these new facts. That in future we must reckon seriously with hormonal factors, may appear from the following example. One of the recent investigators, Viale[27], who looks upon the adrenal as a regulator of the carbohydrate metabolism, found that after extirpation of the adrenals the muscle glycogen after death did not disappear or it disappeared only slowly—even after incubation at 37° C. for several hours—i.e., this glycogen showed a property which we find in glycogen disease. The factors responsible for this change are still obscure.

Our first patient E. showed some clinical symptoms of a disturbance in the function of the hypophysis; these were absent in the second patient B. Neither child showed any abnormality of the chloride metabolism. The reaction of Aschheim-Zondek, performed upon the urine of both patients (Ivens) proved to be negative.

If we accept a hormonal cause for the occurrence of accumulation of glycogen which can be mobilized with difficulty, one asks oneself whether this factor may not always play a rôle in an early period of life. From many experimental observations we know that glycogen occurring in embryonic life and also shortly after birth behaves functionally differently from that in adults, but similarly to that in glycogen disease. We have already put forward the hypothesis, on the ground of an extensive examination of premature children[28], that in our first patient there might be the possibility of the persistence of a foetal condition. It has to be accepted that the factors which during foetal growth influence the local accumulation and the fermentative breakdown of glycogen in organs and under certain circumstances also in later life keep their function and in this way cause a marked hypertrophy by accumulation of glycogen in one or more organs.

An enlargement of the liver by accumulation of glycogen accompanied by hypoglycaemia may be caused experimentally by a certain diet (high carbohydrate with much protein), as has been demonstrated by Schöndorff[29] and Junkersdorff[30]. The latter found that this may succeed most easily in young animals. His conception[31] that these observations must be considered seriously in explaining glycogen disease in man must provisionally, in our opinion, be denied. In the described cases of glycogen disease and in our patients nothing is known of a particular diet which preceded the onset of glycogen liver. For the most part we had to deal with a congenital abnormality. Further, it is highly questionable whether the glycogen which is accumulated in the liver and also in other organs under these experimental circumstances shows the peculiarities of the glycogen in glycogen disease, which during life and after death can be split only with difficulty.

Further clinical and clinical-chemical study of both our patients revealed the following facts. In our girl at the end of May, 1933, the height was 40 inches, i.e., an increase of 3 inches since January, 1932; during the same time her weight increased only from 35½ to 39½ pounds. The maximum abdominal circumference increased only 0·2 in. The bones of the wrist had developed to a greater extent during this time.

In our boy the height at the end of 1931 was 55 inches; in June, 1933, it was 57 inches. During the same time his weight increased from 75 to 95

pounds. He thus gives the impression of corpulence. It is important to state now, at the age of 12 years, nearly all his teeth are still milk teeth. The general condition of both patients is excellent.

As in the case of our boy, we prescribed for the girl a mixed diet rich in carbohydrates, with vegetables and fruit juice and very little fat. In the girl we are again and again impressed by her extraordinary preference for bread. Attacks of severe vomiting, which formerly occurred, occur no longer. In fasting condition, however, the urine aways contains acetone and often also diacetic acid.

During last year we paid special attention to the ketosis in both our patients. In these cases of chronic ketosis were products of ω-oxydation of the fatty acids present in addition to the products of β-oxydation as was discovered by Verkade[32] and his co-workers? The urine of our patients, containing ketone bodies, was investigated for products of this oxydation by Dr. Elzas in Rotterdam with negative results.

Could the ketosis of our patients be influenced by oral administration of choline? This question is of importance in view of the recent investigations of C. H. Best[33] and his collaborators. From these it apepars that a fatty degeneration or a superfluous fat depot in the liver may be prevented experimentally or much decreased by oral administration of choline; the glycogen content of the liver under these experimental conditions is not influenced. These results have been applied already to patients suffering from diabetes mellitus with severe ketosis. In cases of glycogen disease which came to autopsy there has sometimes been found in addition to the very large amounts of glycogen in the liver, much fat (e.g., in the two cases described by von Gierke). What was the effect of the choline on the ketosis and other symptoms in our patients? We obtained the definite impression that during the time that choline* was used from October, 1932, to March, 1933, beginning with doses of 30 mgm. and slowly increasing to 600 mgm. daily, the mean excretion of ketones in both our patients was much lower than before. However, no influence was noted upon the fasting blood sugar, the glycogen content of the blood and the cholesterol content. After stopping the administration of choline the excretion of acetone remained minimal in our boy; even with the most sensitive methods often no acetone at all could be demonstrated in the fasting urine. In the girl the fasting urine usually contains more total acetone and β-oxybutric acid now than it did during the choline treatment.

The girl for many weeks was given small amounts of dried thyroid; no influence upon the metabolism was noted.

As compared with former examinations the most striking changes in our boy are the decrease of the ketosis, which has nearly disappeared, the marked elevation in the fasting blood sugar in the capillary blood already mentioned and the growth. The other abnormalities in his metabolism are present as before. There is still definite leucopenia, a count in June, 1933, showing 4,900 leucocytes. We think that the dimensions of his liver remain the same. After giving extra sugar the urine never contains any sugar.

* Our thanks are due to M. Guggenheim in Basle and also to G. H. Nijhoff, apothecary at Amsterdam (Wilhelmina-Gasthuis) for procuring us the needed choline.

Differential diagnosis.

Are the symptoms of hepatomegalia glycogenica as found in both our patients characteristic for this disease? This question is of great importance in the differential diagnosis from other chronic liver diseases and to a certain extent from those of other organs (e.g., adrenal tumours and kidney tumours). It is also important, therefore, in considering whether in a certain case a laparotomy should be done. Our own experience and recent publications about glycogen disease with marked hypertrophy of the liver give us ground to answer this question provisionally in the affirmative. In hepatomegalia glycogenica there exists a series of symptoms (Table 6) which have never been observed in other chronic liver affections, at least not in this combination, viz., very marked congenital enlargement of the liver, or the same enlargement coming on shortly after birth, an enlargement in which the surface of the liver remains smooth, eventually combined with hypertrophy of other organs but not the spleen; chronic hypoglycaemia in the fasting condition combined with ketosis, after injection of adrenalin absence of or only a slight rise of blood sugar, but increased ketosis; abnormal blood sugar curve after giving different carbohydrates with or without any marked excretion of sugar in the urine.

On the other hand in hepatomegalia glycogenica a series of clinical and clinical-chemical symptoms which are present in other chronic liver affections (especially cirrhoses) are absent, e.g., jaundice, oedema, ascites, haemorrhages, enlargement of the spleen, glycosuria after giving galactose or fructose or both; further, a very marked increase of the globulin content of the blood serum and a strongly positive Takata-Ara reaction, and often a marked decrease of the amount of cholesterol esters in the serum[34, 35]. Certain other symptoms of our patients certainly cannot be regarded as being typical of the glycogen liver; some other symptoms may or may not be. Urobilinuria was constantly absent in the case of the boy but not in that of the girl. The physical infantilism which both our children show is certainly not a typical symptom, neither is the familial character of the disease found by some investigators[36]. A hepatic infantilism may occur in different parenchymatous liver affections as was recently clearly shown by Unshelm[37]. It is important to note, however, that within a rather short time marked increase of growth took place in both our patients. Whether determination of blood glycogen, having regard to the number of leucocytes has any important significance in the differential diagnosis of chronic liver affection in childhood, cannot as yet be told. We are of the opinion, however, that in any case this may very probably hold true for investigating the possibility of splitting of glycogen as was described above.

From the series of cases of hepatomegalia glycogenica which were described recently it was probable, in view of the well-known dissociation of disturbances in liver function, that the intensity of some symptoms and the abnormalities in metabolism may vary, even in the same patient, e.g., the the rise of blood sugar after giving carbohydrate and the degree of acetonuria. In both our patients there are also differences. Pathologically too the picture is not always the same; this is true for instance of the amount of

fat or connective tissue found in the liver which is accumulated with glycogen. In our boy the appearance of the liver as found at laparotomy and his general adiposity indicate that his liver contains much fat, just as in the first case of von Gierke. In the girl the constant urobilinuria and the weak positive Takata-Ara reaction (see above) indicate perhaps, that in her case the connective tissue is more increased (early cirrhosis?), as was found in the second case of von Gierke.

The morbid picture called ' stéatose hépatique massive ' by Debré[38, 39], which is also characterized by a very marked hypertrophy of the liver, beginning at a very early age, and in which biopsy indicates only the existence of a very large accumulation of fat in the liver, may show clinically not only an important difference from, but also a marked resemblance to, the picture of the glycogen liver. It has been described by different authors and was observed as a familial affection by Björum[40] who also gives the results of the autopsy. In this affection glycosuria and hæmorrhages or sudden temporary changes in the size of the liver occur not infrequently. Results of investigations in the metabolism in cases of such enormous fat accumulations in the liver indicate without doubt that the differential diagnosis of hepatomegalia glycogenica and cases of ' stéatose hépatique massive ' may be possible clinically, as by a thorough examination of the carbohydrate metabolism.

On several occasions one had an opportunity of confirming and extending the fundamental facts of glycogen disease, found post mortem by von Gierke and Schönheimer. It appeared that glycogen accumulation could give rise to marked hypertrophy also of other organs than liver and kidneys, heart (see Pompe[41] and also Putschar[42]), pyloric muscle (personal communication, Deelman). We were able to investigate different organs of a baby with idiopathic hypertrophy of the heart, caused by accumulation of glycogen as first described by Pompe. In this case the adrenals were of normal size. We determined the glycogen content of the organs and studied the behaviour of the glycogen in some organs. We compared the results with those in the organs of a baby with very marked hypertrophy of both ventricles in a case of patent ventricular septum. Where the organs were not investigated immediately they were kept frozen. The glycogen content was determined in small pieces of the organs after hydrolysing with HCl (determinations of the glucose after the method of Hagedorn and Jensen). The following results were obtained (percentage figures):—Idiopathic hypertrophy of heart: heart, 7·96; liver, 9·13; spleen, 1·46; muscle, 9·39; lung, 0·034; spinal marrow, 0·583; adrenal, 1·25; blood, 18 mgm. (after death); hypertrophy of heart in patent intravent. septum: heart, 0·055 (L.V.), 0·07 (R.V.); liver, 0·103; kidney, 0·062; spleen, 0·01; muscle, 0·011; blood, 12·75 mgm. (during life). It must be remembered that both infants had passed through a period of fever shortly before death and that the autopsy was performed at least 24 hours after death, therefore, the determinations were done under circumstances in which there would normally be only traces of glycogen in the organs*.

* Our special thanks are due to Prof. de Vries, and to Dr. Hammer, for their kindness in giving us pieces of different organs.

For comparison we give the results of glycogen determinations in some organs obtained by others in cases of glycogen diseases.

Schönheimer[5]:

Liver 10·43 per cent. glycogen in the fresh organ (33·72 per cent. of the dry substance).
Kidney 6·53 ,, ,, ,, ,, ,, (36·82 ,, ,, ,, ,,).

Unshelm[9]:

Liver 14·2 ,, ,, ,, ,, ,, (47·68 ,, ,, ,, ,,).

From our results one sees clearly the enormous increase of glycogen content, not only of the hypertrophic heart, but also of other organs, especially liver and muscle in this case of idiopathic hypertrophy of the heart. In the patient with septum defect in which the hypertrophy of the heart muscle was at least as marked as in the glycogen heart only very small amounts of glycogen were found in the available corresponding organs.

The results obtained in the glycogen heart correspond to those obtained by others in cases in which the hypertrophy concerned liver and kidneys. (Unshelm also found much glycogen in muscles and brain.)

The great stability of the glycogen in glycogen disease was first demonstrated by Schönheimer in autolysis tests. The glycogen isolated from the organs (liver and kidneys) could, however, be split by fermentation; by addition of ground-up liver the glycogen was broken down within a short time. Unshelm demonstrated the same by mixing the ground-up liver of the patient with glycogen disease with ground liver of an adult.

In the glycogen heart we also investigated the stability and possibility of splitting of the glycogen. We investigated the decrease in the amount of glycogen in small pieces of heart muscle, on one hand, after keeping them for 48 hours at 37° C.; on the other, after mixing with the same amount of heart muscle from a patient who died from meningitis, which latter tissue contained only traces of glycogen.

Glycogen heart alone: decrease from 7·86 to 6·74 per cent.
In mixing experiment: ,, ,, 7·86 ,, 1·7 ,, ,,

Even under these conditions so extraordinarily favourable for glycogenolysis, the glycogen in the glycogen heart showed a notable stability which disappeared for the most part in mixing with heart muscle obtained from the meningitis patient.

Summary.

The results of new investigations performed in a boy with hepatomegaly and a particular disturbance in carbohydrate metabolism, formerly regarded as being the expression of an accumulation, especially in the liver, of glycogen which could only be mobilized with difficulty, are described. The investigations in a second case (a girl) with hepatomegalia and the same deviation in metabolism are also reported. The clinical history of this girl is given in detail.

The glycogen metabolism was especially studied in both patients. A method is given of determining the glycogen in 1 c.c. of blood. The question of the cause of the difficulty in splitting glycogen in glycogen disease in general was studied and is discussed. Some new facts of hepatomegalia

glycogenica were established and their value for the differential diagnosis from liver cirrhoses in childhood is stressed.

The distribution of glycogen in different organs and the stability of this glycogen in the heart was investigated in a case of cardiomegalia glycogenica and in a case of hypertrophy of the heart due to a patent septum ventriculorum.

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PATENT INTERVENTRICULAR SEPTUM (MALADIE DE ROGER)

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Roger[1] in 1879 was the first to describe a congenital defect of the heart in which symptoms were absent, although definite, constant, and characteristic physical signs were present. An interesting feature of his description was that his observations were unsupported by an autopsy on the case that he described. However, so definite was the syndrome that Dupré[2], who verified a case at autopsy in 1891, proposed for it the name of 'maladie de Roger.' To this day very little has been added to Roger's description unless it has been by way of confirmation.

As a preface to a discussion of this particular lesion a part of Roger's work may well be quoted[1a]. In his conclusions he finds that:—

> There is a developmental defect of the heart from which cyanosis does not result in spite of communication between the two ventricular cavities . . . It consists of an opening in the interventricular septum. It is revealed only on auscultation by a physical sign with very definite characters; this is a long loud murmur . . . It begins in systole and is prolonged to such an extent as to entirely cover the natural tictac of the heart sounds. It has its maximum intensity not at the apex . . . but over the upper third of the precordial region. It is chiefly medial in position like the septum itself, and from this central position it diminishes in intensity uniformly as one moves the stethoscope over the chest. The murmur is not transmitted to the vessels. It coincides with no other sign of heart disease except a harsh thrill which accompanies it. This murmur is the pathognomonic sign of an interventricular septal defect.

Incidence.—Uncomplicated interventricular septal defects are probably amongst the commonest of all congenital cardiac abnormalities. Unfortunately few statistics are available on this point, for in most published returns of heart disease, such as those provided by school authorities, cases are all grouped together as congenital heart disease without attempt at separation into different anatomical groups. Apart from the more formal statistics, such as those coming from clinics, evidence of the incidence of this abnormality is scanty. This is because the maladie de Roger is so benign and symptomless that many cases never come under observation, and still fewer to autopsy.

In a series of 119 cases of congenital heart disease in elementary school children described by Perry[3], if his Groups 1 and 2 are taken together, 42 cases (35 per cent.) may be presumed to be instances of uncomplicated septal defect. As evidence of the benign nature of this defect it is noteworthy that practically all his cases were on full school régime with games and drill. In Abbott's[4] 850 collected cases a defect of the interventricular septum was present 240 times. An associated abnormality was present in 186 cases, so that 54 cases had a septal defect as the primary lesion. In 8 of these cases the aorta over-rode the septal defect, so that pure patency of the interventricular septum occurred 46 times. Laubry and Pezzi[10] state that pure patency of the septum is rare, and in view of the origin of the defect from arrest of development of the bulbus cordis, suspicion of concomitant pulmonary stenosis must always be aroused. They are inclined to think that the diagnosis is too frequently made. As each of the cases of Abbott has been controlled by autopsy, they have confirmed the work of Roger published many years before.

In the present communication uncomplicated cases only are considered. Cases in which there is dextra-position of the aorta, on account of the large venous arterial shunt that is necessarily present, properly belong to the cyanotic group of congenital cardiac cases. The syndrome of ventricular septal defect, right-sided aorta, and no stenosis of the pulmonary artery, has been named the Eisenmenger complex. It seems probable that a few of the cases described as the maladie de Roger, but with cyanosis, belong to this group.

Pathology.—The defect arises as a fault in development of the bulbar septum which does not descend sufficiently to meet the ventricular septum, and consequently the defect is usually situated at the upper part of the interventricular septum. Letulle has supported the view that patency of the interventricular septum is most frequently the result of a fœtal endocarditis, but this view has received very little support.

Usually the defect is very small, admitting only a probe, but sometimes the opening may be large enough to admit the thumb. It is most commonly just anterior to the membranous part of the septum, the undefended space of Peacock, and as it opens immediately beneath the septal cusp of the tricuspid valve the latter structure may occasionally be involved, producing tricuspid insufficiency. Occasionally other parts of the septum may be the site of perforation. In consequence of this communication between the two ventricles there is an arterial venous shunt of blood from left to right. Under some circumstances, notably pulmonary infection, or as a terminal event, reversal of flow may occur with resultant cyanosis (cyanose tardive). Certain observers have recorded cases in which there was permanent cyanosis. These cases would appear to be outside the limits of the disease as defined by Roger, and are probably, as indicated above, the result of dextra-position of the aorta.

Complications.—Patients with this abnormality, as all others with congenital cardiovascular defects, are exposed to the risks of the supervention of an infective endocarditis. The proportion of cases in Abbott's

series where such an event occurred was 37 per cent., and vegetations when present may be found in the margins of the defect, and on the wall of the right ventricle where the stream of blood passing through the defect impinges. Audibert[18] and others in recording a recent case of the maladie de Roger where such an event occurred emphasized the great rarity of these cases, and expressed the opinion that the congenital cardiopathies in general, and lesions of the interventricular septum in particular, were not nearly as susceptible to the onslaught of streptococci as healed rheumatic lesions of the valves.

An interesting abnormality described as being associated with defects of the interventricular septum is congenital heart block. Scattered through the literature are numerous references to congenital heart block, and a number of these cases have been attributed to congenital perforations of the interventricular septum, at the site of the undefended space of Peacock which is in intimate relationship with the bundle of His. Such a hypothesis has always been attractive, and has often served to explain the pathology of these cases where no autopsy has been performed. If, indeed, a simple perforation of the interventricular septum at this site were the sole explanation of congenital heart block, then such cases should be common in view of the frequent occurrence of ventricular septal defects either alone, or complicated by other congenital abnormality. In Lampard's[5] collected series of 31 cases of congenital heart block, congenital cardiac lesions were present in 19, and of these 12 were apparently due to a patent interventricular septum. Aitken[16] has reviewed 39 cases of congenital block, and has found 25 cases in which a patent interventricular septum was reputed to be present. More recently Yater, Lyon, and McNabb[6] have reviewed 44 cases of accepted congenital heart block, and of these a patent interventricular septum was present in 26, and complete absence of the septum in one. The relation of the bundle of His and its branches in cases of septal defect has been investigated by Monckeberg[8]. In general there has been very little change in the normal arrangement of the fibres. Even in extreme types such as the cor biloculare the bundle has been found on the wall of the common ventricle dividing into right and left branches, and in Wilson and Grant's[7] case of cor biatriatum triloculare the bundle was present in the tag of tissue representing the interventricular septum.

In explanation of the rarity of conduction defects in these cases the site of perforation is important. In septal defects the usual site according to Abbott is 'at the base of the septum just anterior to the pars membranacea.' Further, the work of Monckeberg suggests that development of the cardiac septa takes place after the development of the bundle of His. The rudiments of the bundle are visible at about the fifth week, but the septa are only visible from the seventh to tenth weeks. It thus seems hardly likely that malformations of the septum will interfere with the development of the bundle that has already taken place. On these grounds it may be argued with some justification that however severe a defect may be present, it probably cannot by itself be the cause of congenital heart block.

Aitken[16] has suggested that the cause of the heart block may be due to an excessive formation of fibrous tissue between the auricle and ventricle which interferes with the continuity of the bundle. On the above grounds it will be appreciated why cases of congenital heart block are rare in practice. If septal perforations alone were sufficient to cause it, this abnormality would be much more frequent than it is, because septal defects are among the commonest of all congenital heart disorders. No case of heart block has occurred in our series.

On theoretical grounds simple patency of the interventricular septum should not be a serious handicap, apart from the risk of a superadded infective endocarditis. The average duration of life in Abbott's cases was but 14 years, the oldest being 44. In this connection it must be realized that Abbott's cases all came to autopsy. The maladie de Roger is so benign and symptomless that probably only a very small proportion of cases are definitely recognized. Owing to a mistaken idea that the congenital cardiac is necessarily young and cyanotic, and over-emphasis of the doctrine of carditis without arthritis, it is probable that many cases pass through life with a diagnosis of a rheumatic heart, or even mitral regurgitation despite the presence of a clear cut clinical picture.

Symptoms.—There are no symptoms that can be properly attributed to this malformation. Its characteristic feature is absence of symptoms with marked physical signs. Cyanosis does not occur except as a terminal event, or during a severe pulmonary infection. Rarely it has been recorded as occurring on exertion, as, for example, in two cases in Perry's series. It was marked in a case described by Carpenter[9]. Holding the breath or the use of a spirometer has not induced cyanosis in any of our cases with this lesion. Dyspnoea on exertion is rarely complained of by the patient unless he is suffering from some added complication, or has an over-anxious mother. The condition is absolutely compatible with a normal school life and participation in games and drills.

Physical signs.—The distinctive murmur has been aptly described by Roger. An extract from his description is quoted above. A long harsh mesocardial murmur occupying the whole of systole, and sometimes slightly prolonged into diastole, with maximum intensity in the third and fourth left interspaces close to the sternum, is the characteristic physical sign. The murmur is conducted with diminishing intensity towards the apex and left clavicle. It may be heard in the neck in a few cases. Frequently it may be heard in the left side of the back, particularly in the left inter- and infra-scapular regions. Its important characteristic is its dimunition in intensity as the periphery of the praecordium is approached. In a few cases there is no definite point of maximum intensity of the bruit; or it may be heard best as high as the second rib and interspace, or low down the left sternal border. In about a third of the cases (15 in 46 cases in Abbott's series), there is an accompanying systolic thrill which may be diffuse, or localized to the point of maximum intensity of the bruit. The thrill may

best be felt, and occasionally only felt with the subject in ventral decubitus. Laubry and Pezzi[10] have described a certain character of the first sound of the heart recalling the first sound in mitral stenosis. The pulmonary second sound is as a rule unaltered, but hypertension in the pulmonary circuit may lead to its accentuation or reduplication.

Certain cases are on record (Parkes Weber[21], French[22], Stamm[23]), in which a thrill and systolic bruit present in early childhood have quite disappeared with the growth of the child. Such a disappearance of physical signs could be explained on the grounds that a lesion of the interventricular septum in a small child may be considerable in relation to the size of the heart and the whole body. If the defect does not enlarge in proportion as the child grows, it may become so small as to be negligible and give rise to no physical signs. Weber also states that occasionally septal defects are surrounded by considerable fibrous tisue which may contract. Bard[20] discussing lesions of the interventricular septum states that the murmur may be absent when pressure within the right ventricle is the same as to that in the left, and consequently there is no flow of blood from left to right.

Radiology.—There is some confusion in the literature as regards the radiological appearance in this condition. This confusion has probably arisen in relation to the degree of the defect. A large defect is a priori more likely to produce changes in the outline of the heart than a small one. Vaquez and Bordet[11] described in certain cases a general increase in the size of the heart as a whole, so that the heart projects on both sides of the mid-sternal line, and appears more or less rounded or globular. They noted vigorous and synchronous pulsation of both borders of the heart shadow. They did not find these changes to be constant: in fact, in certain of their cases there was no apparent alteration in the size and contour of the heart. Laubry and Pezzi[10] describe a similar heart outline in some cases. They, like Vaquez and Bordet, find that there is no abnormality of the vascular arcs. Laubry[12] has later taken up the position that the cardiac contour is as a rule unchanged from normal. Deneke[13] described a globular heart with a spherical pump-like action. Pulsations of abnormal amplitude, visible and synchronous on both right and left borders, takes place. This is, however, of doubtful diagnostic value, for it may be seen in normal children or young adults with a vigorously acting heart. All observers would seem to agree that there is no abnormality of the vascular arcs. The general consensus of opinion appears to be that there is no characteristic and distinctive modification of the cardiac silhouette in this condition. If, however, decompensation sets in, there are suggestive changes in the contour, according to which side of the heart is particularly involved. A large globular heart should always be considered in the light of a ventricular septal defect.

The electrocardiogram is physiological. There may be an increased amplitude of the QRS complexes such as may occur in any other congenital cardiac lesion.

Diagnosis.—There should be very little difficulty in diagnosis as the murmur is characteristic. Points in favour of the diagnosis other than this typical bruit are the absence of any cardiac symptoms, or of a history of rheumatic infection past or present. The bruit is typically mesocardial, is long and harsh with maximum intensity in the third and fourth left spaces close to the sternum. It diminishes in intensity as the periphery is approached.

In cases with a patent ductus arteriosus, the murmur is typically of a continuous or machinery character, maximum in the second left space, with dilatation of the pulmonary artery evidenced by Gerhardt's dullness and by radiological examination. In young subjects with a patent ductus the bruit may be systolic in time, but its maximum intensity is always in the second left interspace, and again evidence of dilatation of the pulmonary artery is forthcoming (Muir and Brown[13]).

In pulmonary stenosis cyanosis may not appear until late and the case be quite symptomless. The bruit is entirely systolic in time, maximum in the second left space, with modification of the pulmonary second sound which is diminished or absent. Radiological examination shows fullness of the pulmonary arc.

From septal defects complicated by dextra-position of the aorta, distinction is made by the early appearance of cyanosis and the prominence of dyspnoea. Similarly in the tetralogy of Fallot cyanosis, clubbing, and dyspnoea are present; the bruit is conducted into the carotids, and there is a characteristic radiological picture (Papp[14]).

In tricuspid insufficiency, which may be associated with a septal defect, the murmur is loudest to the right of the sternum, the right side of the heart is dilated and the liver is enlarged. Cardiac failure is early and prominent.

Functional or haemic murmurs are best heard at the apex or over the pulmonary artery. They are soft and blowing, and tend to vary with the phase of respiration and the position of the subject.

From rheumatic heart disease diagnosis is made by the absence of history of rheumatic infection, arthritis or chorea. The youth of the subject and the early recognition of the heart lesion may often be helpful points in coming to a decision. In rheumatic disease of the mitral valve the bruit is loudest at the apex and is conducted to the axilla. There is also modification of the heart sounds. The systolic bruit is not so prolonged and has not the elective localization of the bruit of a septal defect.

Treatment.—Roger in his original publication naively writes:—

> An exact diagnosis in heart disease ordinarily demands an active and persistent treatment. If, on the other hand, there is a congenital malformation of the heart vigorous treatment is useless and even harmful. To show, thanks to precision in diagnosis, when to act in one case, and refrain in another is to render a service not only to physicians but also to patients[19].

Little may be added to this. These cases require no treatment other than abstention from coddling and the careful eradication of any septic

focus that may be present. These children should be allowed to live a perfectly normal life unrestricted. Accurate diagnosis and careful explanation of the nature of the disorder will go a long way to reassure parents and patient, and prevent the development of a cardiac invalid.

Authors' series.

In our present series of 100 cases of congenital heart disease in elementary school children, 40 appear to have a patent interventricular septum as their sole abnormality. In arriving at a diagnosis we have adhered strictly to the clinical description of Roger, and have employed subsidiary methods of investigation to exclude other possible malformations. In all cases teleroentgenograms have been taken and some have been examined under the screen. In view of the youth of our patients, and their dislike to being in the dark, the former method is our method of choice, although it is open to some objection on the ground of accuracy. In a few cases electrocardiograms have been taken. We have accepted as the essential points in diagnosis the symptomless nature of the malady, and its marked physical signs. We have interpreted a harsh, prolonged, mesocardial systolic murmur of maximum intensity in the third and fourth left interspaces close to the left sternal margin as the capital physical sign. This bruit is so characteristic that, once appreciated, it need never be confused with other bruits, particularly with those of a functional or haemic character.

Sex and age.—Of our 40 cases 25 are females and 15 are males. We can offer no adequate explanation of the apparent preponderance of females, but we find that in our whole series of congenital cardiac cases the female cases are somewhat in excess. There are 54 per cent. females in the whole series, but this does not explain the percentage of 62·5 females in the series under discussion. The youngest is a male aged nine months, and the oldest a male of 14 years. The first intimation of the presence of a cardiac lesion was at the routine school entrance examination in 28 cases. Of the remainder, in only 1 case was the lesion recognized at birth. In 11 cases the abnormality was discovered during some illness, such as influenza, measles or pneumonia. The early recognition is of some importance in diagnosis because the main incidence of rheumatic carditis is after the age of 5 years, and hence the earlier the age of detection of a cardiac lesion, the more likely it is to be of congenital origin.

Associated abnormalities.—Two cases were mongols, and 1 case had an absent xiphisternum. We have been particularly careful to search for associated developmental defects in these cases and have been struck by their rarity.

Symptoms.—Two cases were said to have been blue babies at birth. One case, which was said to have 'attacks,' probably was suffering from minor epilepsy. The large proportion of these cases are quite devoid of symptoms referable to a cardiac condition. One case complained of

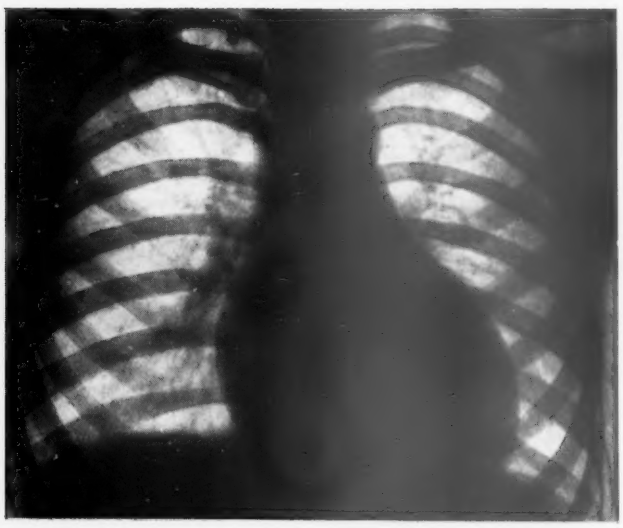

FIG. 1.

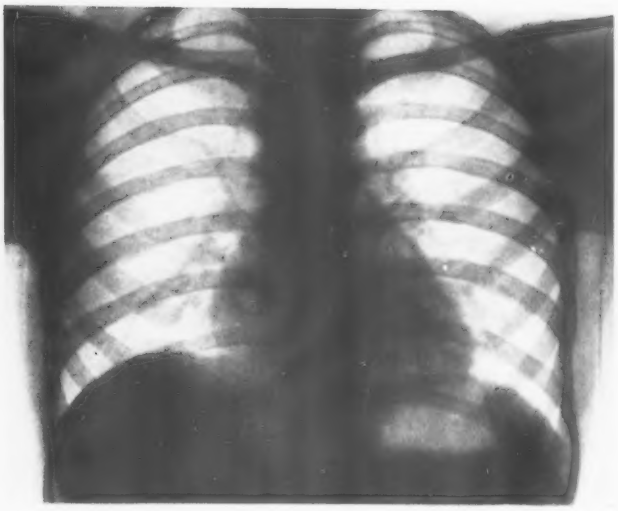

FIG. 2.

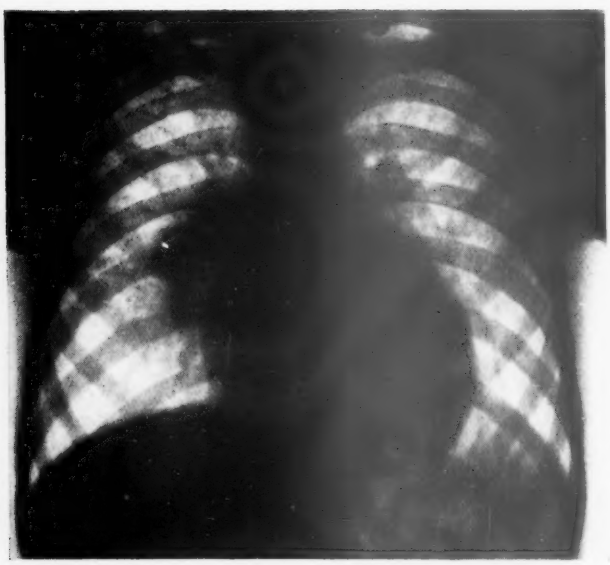

FIG. 3.

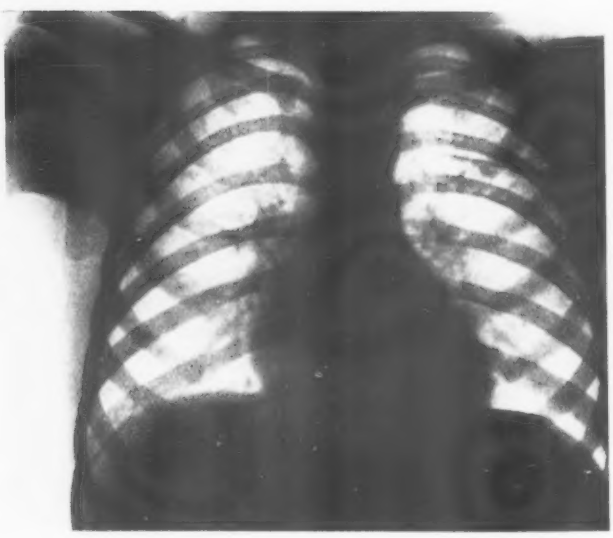

FIG. 4.

The heart in the maladie de Roger. Skiagrams of typical cases showing a globular contour.

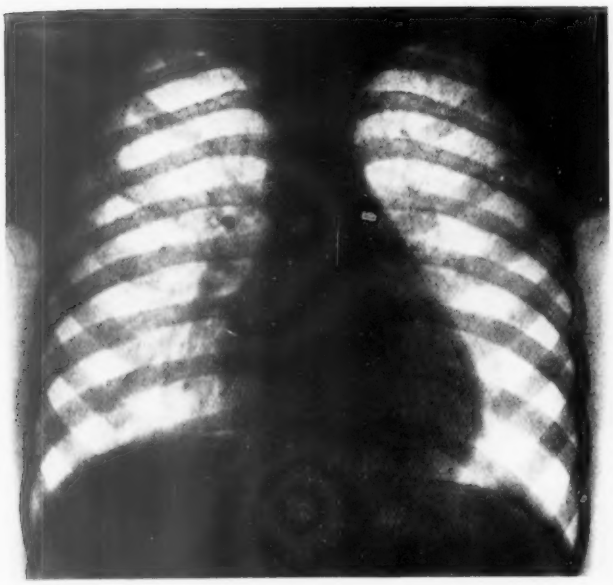

FIG. 5.

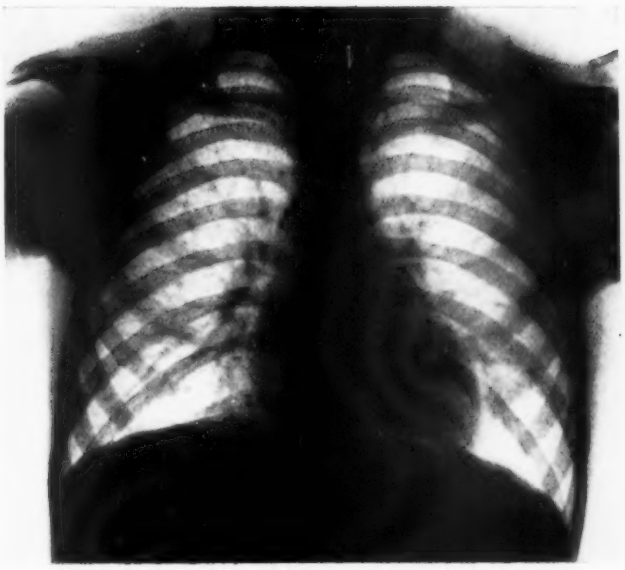

FIG. 6.

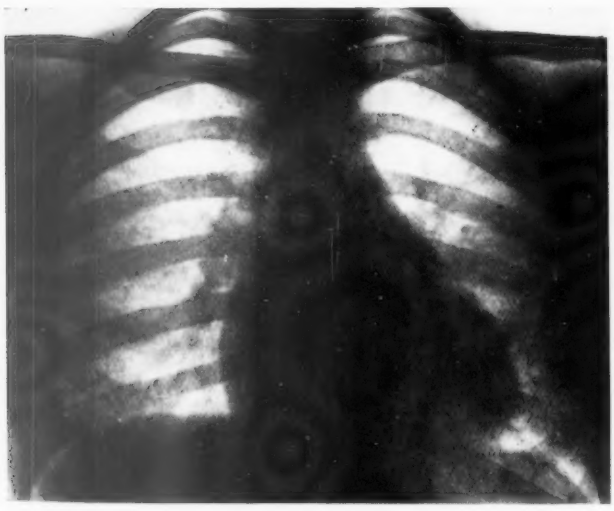

FIG. 7.

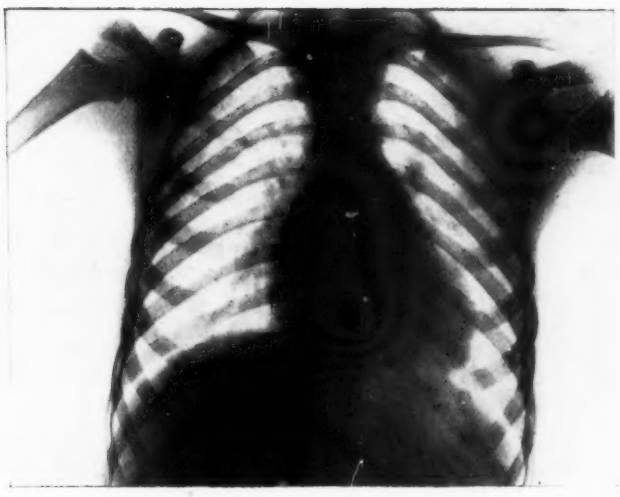

FIG. 8.

The heart in maladie de Roger. Typical cases with a straight left border.

dyspnoea on exertion, and another of palpitation. We find it difficult to assess the importance of these symptoms in children, because some of the symptoms are occasionally due to a dislike of the school that they are attending, and clear up with a change of school. Cyanosis appears in the histories of 5 of these cases, and in only 2 cases does it appear to have been important. In one case, the child was for a period the colour of Reckitt's blue. This cleared up, and this child who is seen regularly is now quite devoid of cyanosis, and presents the typical clinical picture of Roger's disease with no radiological abnormality. In another case cyanosis on exertion was sufficient to call for remark by her parents, but such cyanosis has never been reproduced in the clinic. In the others cyanosis has only been transient and occurring with respiratory infection. As far as could be ascertained there is no increased liability of these children to respiratory infection. All the children were weighed and measured and their heights and weights were compared with normal standards for school children. Twelve of the children were definitely above the average development, 18 were average, and only 10 were below average.

Physical signs.—A loud harsh prolonged systolic bruit was present in all of the cases. In 15 it was maximum in the third left interspace close to the sternum, in 20 in the fourth left space, and in 4 low down between the apex and the left sternal border. In one case where the murmur was loud in front it was definitely louder in the left interscapular region behind. There was no evidence in this case of a coarctation of the aorta. In 12 of the cases the murmur was audible in the left side of the back. We have not followed the example of Perry[3] and segregated these latter cases into a separate group as we have felt that fundamentally they all belong to the same group. It seems possible that the site of perforation of the septum may affect the distribution of the murmur. This is suggested by the case of Weiss quoted by Abbott[17]. Similarly, we have thought in 4 cases in which the maximum intensity of the bruit was midway between the apex and the left sternal border, that the septal perforation was abnormally placed. In 5 cases the bruit was audible in the carotids. It has been generally stated that the bruit is not audible in the neck, and that audibility in the neck is a capital point in the diagnosis of the tetralogy of Fallot. In a pure pulmonary stenosis the systolic bruit is not heard in the carotids, whereas the coincident presence of a septal defect with over-riding of the aorta renders conduction of the murmur to the neck possible. None of these 5 cases show any dextra-position of the aorta radiologically, or any cyanosis. In 13 cases (32 per cent.), a systolic thrill was present and its maximum intensity was at the site of maximum intensity of the bruit. In 2 cases the thrill was present at the first examination, but not on examination at a later date.

Radiology.—All our cases have undergone X-ray examination. We have as a routine taken teleroentgenograms of these children at a distance of seven feet. We have found this method preferable for reasons indicated

above. Radiological examination has failed to disclose any typical constant cardiac contour which might justly be said to be characteristic of the maladie de Roger. In a large number of cases the heart outline has appeared to be quite normal, and in only 12 cases could the heart be said to approach a globular contour (Figs. 1, 2, 3, and 4). The pulmonary arc is full in certain instances, giving a rather straight left cardiac border (Figs. 5, 6, 7, 8). In the cases examined with the fluorescent screen, the vigorous spherical pump-like action of the heart, described by Deneke, was not consistently seen. Our impression is that such vigorous synchronous contraction of both borders of the heart can be seen not infrequently in children with apparently normal hearts. Particular attention has been paid to the vascular arcs in a search for dextra-position of the aorta and right aortic arch.

We have found the X-ray examination of most value in excluding other congenital cardiac conditions.

Summary.

(1) A study has been presented of 40 cases in which the physical signs pointed to a diagnosis of the maladie de Roger.

(2) Evidence has been brought forward which seems to indicate that this condition is much commoner than is generally recognized. A proper appreciation of the physical signs as described by Roger would lead to the more frequent identification of this defect.

(3) In the present series there was no case of heart block or of infective endocarditis. The suggestion is put forward that a lesion of the interventricular septum per se is not the whole cause of congenital heart block.

(4) Permanent cyanosis is not a part of the clinical picture of the maladie de Roger. When cyanosis is permanently present it is due to some accompanying structural abnormality.

(5) There is no characteristic radiological picture of the maladie de Roger.

Our thanks are due to Dr. Morrison and the Assistant Medical Officers of the Hull School Medical Service, and to Dr. Southey, of the Grimsby School Medical Service, for referring these cases to us; and to Dr. Bannen and Mr. S. V. Dolby for the radiograms.

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FAMILIAL SEX-LINKED ECTODERMAL DYSPLASIA WITH INCOMPLETE FORMS

BY

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AND

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Ectodermal dysplasias have both a clinical and a genetic interest. A number have been reported, but we have still much to learn about them, and since they are so rare our knowledge of them can only be furthered by accurate records of individual cases. The present case with its pedigree, therefore, is being recorded.

There is no need to review the literature, for this has been done by a number of recent writers (Janitzkaja and Rjabow[8], MacKee and Andrews[10], Smith[13], Parkes-Weber[15], Weech[17], and notably Cockayne[2]), but to assist in tracing similar cases a few of the more important references have been given.

Case report.

E. G., aged 14 years, was brought up to the dental department of King's College Hospital for advice about his teeth. Something of his appearance may be judged from his photographs (Fig. 1 and 2). In physical and mental features he is similar to other cases reported. In intelligence he is normal, if anything above normal.

TEETH AND JAWS.—The boy has only had five teeth. When first seen, one was merely a decayed fragment which has now been removed. The other four are conical, strong teeth, standing in the four canine situations and occluding with one another (Fig. 1 and 3). They are not truly homologous with any normal tooth, being quite conical. The enamel ends in a strong unfestooned ring, and the root is single, strong and well developed (Fig. 3 and 4). The fragment was also single rooted.

The gums are firm and healthy and the periodontal membrane and supporting alveolus are normal radiographically.

There is no history of any other teeth and the present ones did not commence to erupt till the age of five. The alveolar bone of the jaws has no enlarged areas suggestive of erupting teeth, and, excepting round the standing teeth, measures nowhere more than one-eighth of an inch across, and has a hard smooth edge. Radiographs show no trace of other teeth, tooth germs, or empty sockets; and, excepting round the teeth, calcification of the alveolus seems very poor. This is well shown in the radiographs (Fig. 4 and 6).

The plan of his jaws is normal in outline, the four teeth defining the corners. The angle of the jaw is obtuse, the horizontal ramus merging gently into the ascending part (Fig. 5).

The boy has the typical nutcracker face associated with edentulous mouths, and this, with the ill-defined angle of the jaw, the thin hair, and the elongated cranium, give him a prematurely aged appearance. There are no clefts in lip or palate.

The boy's mouth is always dry since the saliva is scanty, and so he finds it difficult to chew and swallow dry foods and sweets without the aid of water. He is consequently very fond of spiced and highly-flavoured foods.

HAIR.—The hair over the head is fine and dry and first appeared at the age of 18 months. He has no eyebrows (Fig. 1), and almost white eyelashes. No lanugo hair is visible over his body, and none has appeared yet in the pubic and axillary regions. A few hair follicles were found in a section of skin from the anterior aspect of the arm above the elbow.

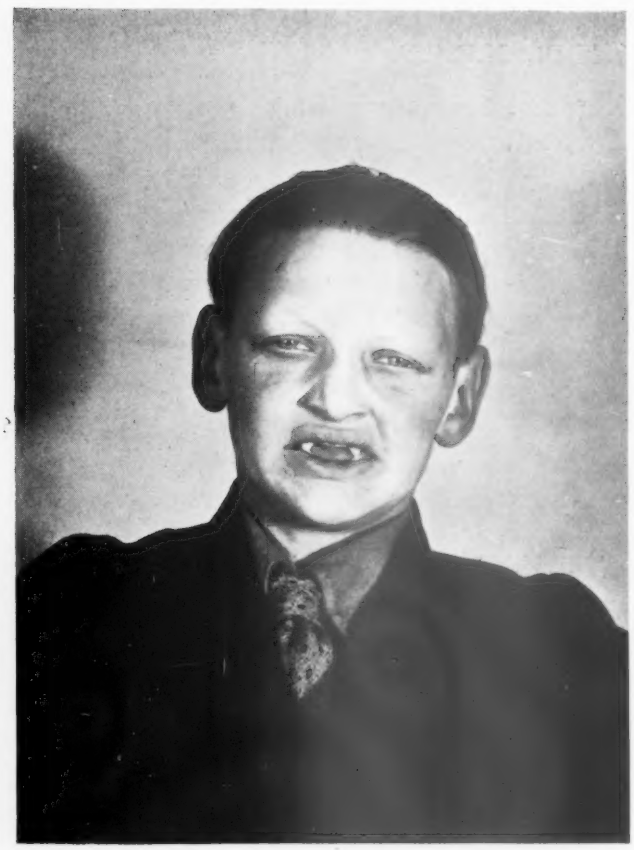

FIG. 1.

FIG. 2.

EYES.—The boy cries normally and vision is six-sixths. No abnormality was was discovered in the lens, vitreous or retina. There is slight proptosis.

NOSE AND THROAT.—The boy has a hoarse voice which becomes worse after talking for some time. He has the saddle nose with depressed bridge which has been reported in other cases (Fig. 2), but his nose has been broken by injury which may partly account for its shape. Internally the nose is roomy, and there is atrophy of the nasal, nasopharyngeal, pharyngeal and laryngeal mucous membranes with some crusting. The sinuses are normal.

SKIN.—The skin is fine and dry and the boy has never sweated. There are no sebaceous papules on the face. The nipples are rudimentary and unpigmented and no gland tissue can be felt. A small portion of skin was taken for examination from the anterior aspect of the arm above the elbow and reported on as follows:—' Sections

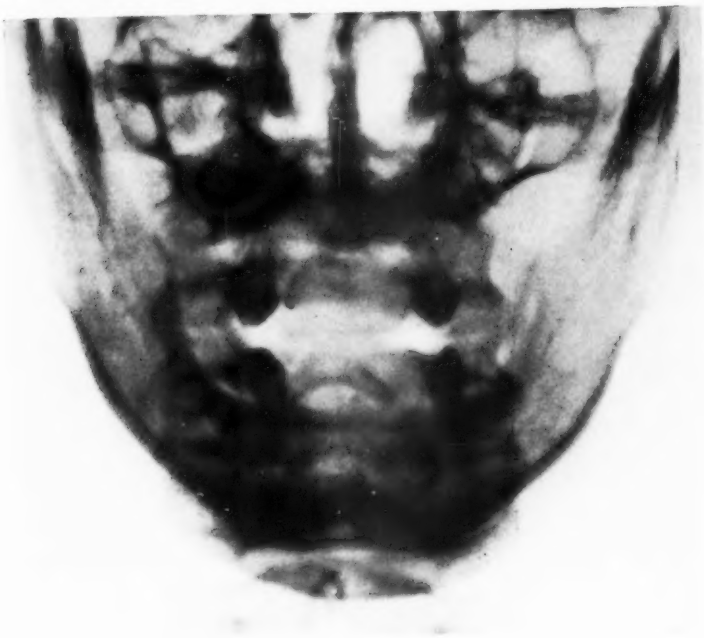

FIG. 3.
Antero-posterior.

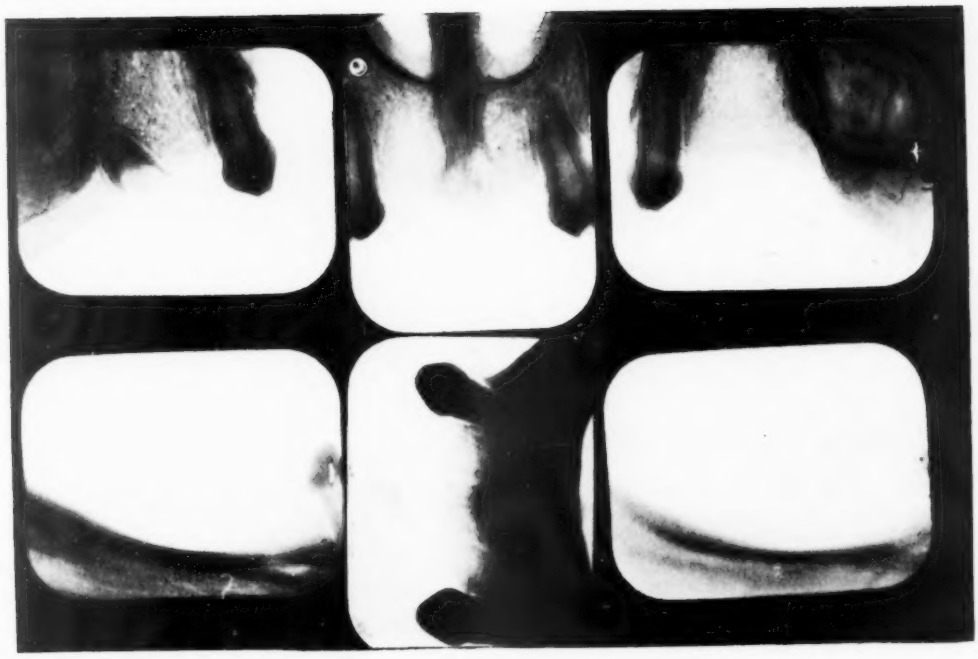

FIG. 4.

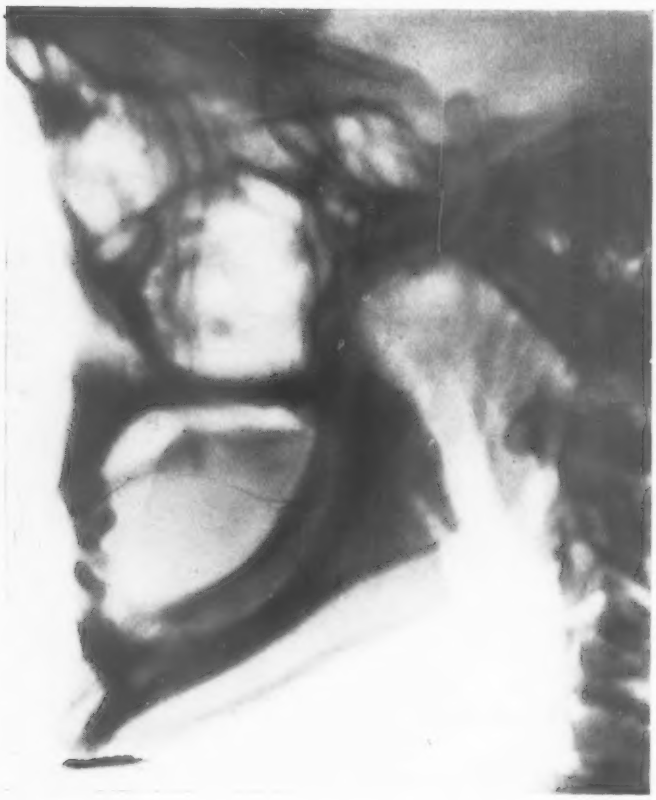

FIG. 5.
Lateral.

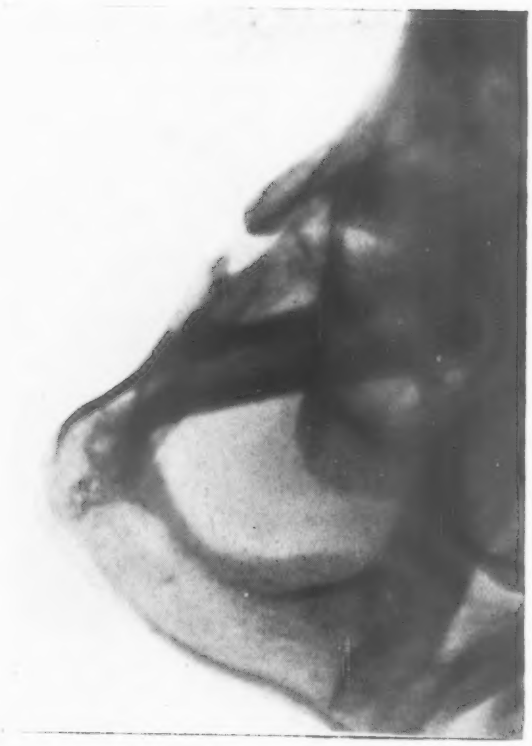

FIG. 6.

of the skin show a very stratified epithelium with a few very small papillæ. There is a little keratin on the surface. No sweat, and only one sebaceous gland is seen, but a few hair follicles are present. In places there is a little lymphocytic infiltration.'

The nails are rather brittle, and have some longitudinal furrows, but are practically normal, and in another case would attract no attention.

TESTES.—The testicles are normal in shape, size, and position.

BONES.—The supra-orbital ridges are pronounced and exaggerated (Fig. 2). Radiographically the long bones were reported as normal, but the sella turcica as small.

BIOCHEMICAL INVESTIGATIONS.—The Wassermann reaction is negative. Blood phosphorus: 4·4 mgm. per 100 c.c. Serum calcium: 9·8 mgm. per 100 c.c. Serum phosphatase: 0·71 units. This last is definitely over the normal, but by itself may have no significance. Salivary juice produced by an acid drop contained abundant diastase.

The gastric residue was found to contain 0·265 gm. free HCl per cent., and 0·385 gm. of total acid as HCl per cent., which indicates a definite hyperchlorhydria.

Previous History.—As in all persons without sweat glands, the boy all his life has had the greatest difficulty in keeping cool. He has had the following illnesses:—diptheria twice, scarlet fever twice, measles three times. He has also been the victim of numerous minor illnesses and has had a broken nose and leg.

Family History.—(see Fig. 7). The child has one sister who is normal. The father and all his family are stated to be normal. The mother's brothers and sisters are all normal. The maternal grandfather and one great uncle, who are both alive and have been seen and examined, have both had deficient sets of teeth. The

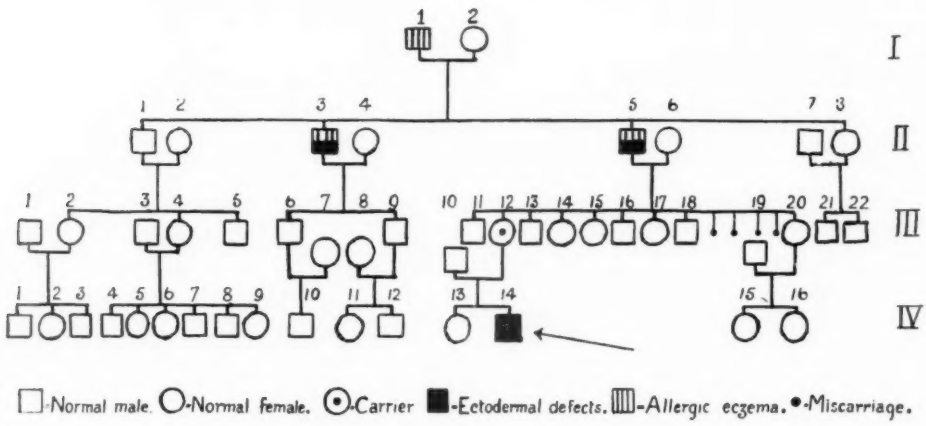

FIG. 7.

IV.	14.	The patient.
III.	10.	The patient's father, one of a small family which cannot be traced.
III.	12.	The patient's mother, who must have been a carrier.
II.	3 & 5.	Both men had a shortage of teeth, but sweated normally. Both, especially II, 3, have suffered from ' allergic eczema.'
II.	6.	One of a family of eight (5 F. and 3 M.), the father and mother of whom were normal. No abnormality of skin or teeth can be found in this family or its descendants, of whom 54 can be traced.
I.	2.	One of a family of six (3 F. and 3 M.). All are remembered as normal. Eight normal descendents can be traced.
I.	1.	Said to have had a skin disease like II, 3 and 5, all his life. Known to have had a good set of teeth when he died and to have sweated normally. One of a family of six (3 M. and 3 F.). No abnormality can be traced in the seven known descendants.

grandfather has only had 13 permanent teeth, most of which were preceded by deciduous teeth. The great uncle has had only 10 permanent teeth, preceded by 10 deciduous teeth, 6 in the upper and 4 in the lower jaw. It is impossible to be absolutely certain about the dentition of either of these men, as the teeth have mostly been lost by disease, but undoubtedly there was a deficiency. Both have also been troubled by an eczema which they inherited from their father, but in other ways they have been normal, and sweat profusely. No other allied abnormality can be traced in the family and as both grandparents are alive and most of the family live locally we have had favourable opportunities of investigating this.

There have been no consanguineous marriages.

Discussion.

Clinically this appears to be a typical case of ectodermal dysplasia of the major type as described by Cockayne and others.

Deficiency of teeth being so rare it is almost impossible not to associate the grandfather's and greatuncle's condition with that of the boy and this makes the case one of the sex-linked recessive type; but the unusual feature of this family history is the incompleteness of the defect in the older generation, and the complication of the allergic eczema.

Gibbs[4, 5] reported that some members of his family group had deficient teeth, and implied that in them the defect was not fully developed, but the report is unfortunately not very detailed.

Although, therefore, the present case introduces a complication into the genetic aspect of the disease, it may ultimately help to throw light on its transmission by having drawn attention to an unusual, or possibly merely neglected, feature.

The authors acknowledge with thanks the help they have received from the photographic and other special departments of King's College Hospital. One of them (R. A. McC.) is indebted to the Medical Research Council for a part-time grant.

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ARTERIAL PRESSURE IN NORMAL SERBIAN CHILDREN

BY

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The question of arterial pressure in the normal child has been the subject of many studies, but there is no great uniformity in the results recorded. The facts that the various writers did not measure the arterial pressure in children of exactly the same age, nor use the same apparatus, explain the divergence in the results recorded. Further, hygienic conditions, feeding and climate in the various countries, play an important part in development, and thus exert an influence on the arterial tension in children even of the same age. Differences in technique, anatomical anomalies, and sometimes an insufficient number of examinations, account also for the varying results obtained.

In the present investigations, from 1925 until the end of 1932, there were examined 840 normal and healthy children of both sexes between the ages of 4 and 15 years; 230 of these children were patients in the Anglo-Jugoslav Children's Hospital in Belgrade, 360 were school children of both sexes from 6 to 10 years, and 250 were school children from 10 to 15 years.

The children were all examined in the recumbent posture and the observations were made on the right arm. Two types of apparatus were used:—the Vaquez-Laubry manometer (auscultatory method), and Pachon's oscillometer. With the Vaquez-Laubry apparatus armlets of two sizes were employed:—for children of 4 to 11 years one of 5 cm., and for children of 11 to 15 years one of 12 cm. The ordinary model of the Pachon oscillometer was employed with an armlet measuring 8 cm. in width.

Vaquez - Laubry apparatus.—With this apparatus the maximum blood pressure in boys measured 101·5 to 122·5 mm., and the minimum from 70 to 95 mm. In girls the maximum pressure varied from 100 to 125 mm., and the minimum from 72·5 to 85 mm. The differential pressure measured about 30 mm. (Table 1 and Chart I).

From a study of these results the following facts emerge. The maximum and minimum pressures in Serbian children of both sexes are inclined to increase as the child grows older. There is also a slight increase in the differential pressure, especially in girls after the age of 7 years. It is interesting to note, too, that there is a somewhat more definite increase in the maximum and minimum pressures between 12 and 14 years in both sexes, the age of puberty; and that the maximum pressure in girls of 13, 14

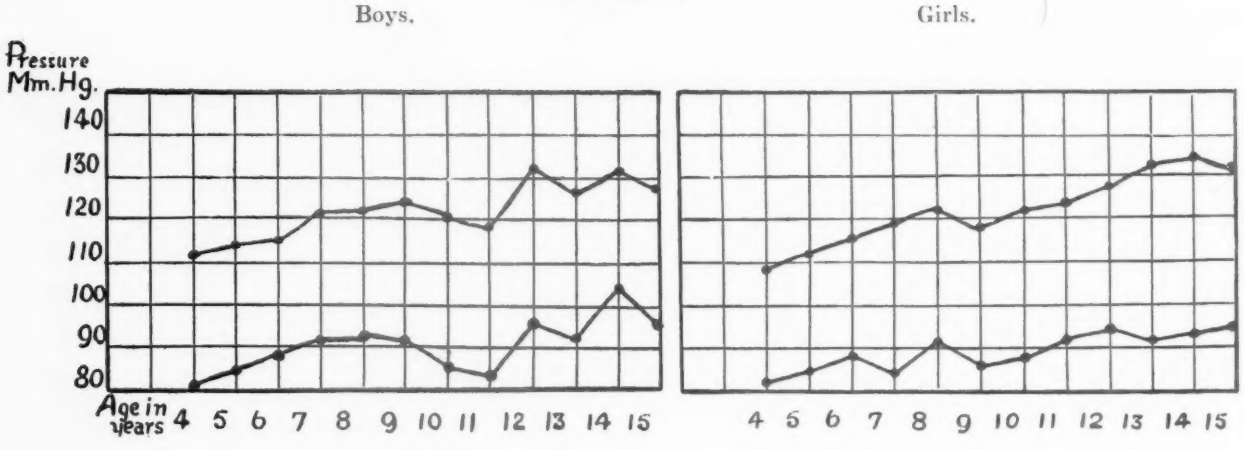
TABLE 1.

ARTERIAL TENSION, ACCORDING TO AGE, MEASURED BY THE VAQUEZ-LAUBRY APPARATUS.

No. of Cases.	Age.	Boys.			No. of Cases.	Girls.		
		Max.	Min.	Per cent. difference.		Max.	Min.	Per cent. difference.
24	4 years	101·5	70·0	31·5	26	99·5	71·5	28·0
30	5 ,,	104·7	74·2	30·5	35	102·5	75·5	27·0
50	6 ,,	105·5	79·0	26·5	40	105·3	79·0	27·3
55	7 ,,	110·6	80·7	29·9	45	109·7	77·0	35·7
48	8 ,,	111·5	82·5	29·0	57	112·0	81·0	31·0
43	9 ,,	113·0	80·7	32·6	52	107·5	76·0	31·5
46	10 ,,	110·0	76·0	34·0	42	112·5	77·5	35·0
27	11 ,,	109·0	72·5	36·5	30	117·0	81·0	33·0
26	12 ,,	122·5	87·0	35·5	29	118·5	85·6	32·9
28	13 ,,	116·5	83·0	32·5	26	123·5	82·0	41·5
22	14 ,,	122·5	95·0	27·5	23	124·5	83·0	41·5
18	15 ,,	117·5	84·5	33·0	18	122·5	84·0	38·5
417					423			

Medium value.

CHART I.



Blood pressure measured with Vaquez-Laubry apparatus according to age.

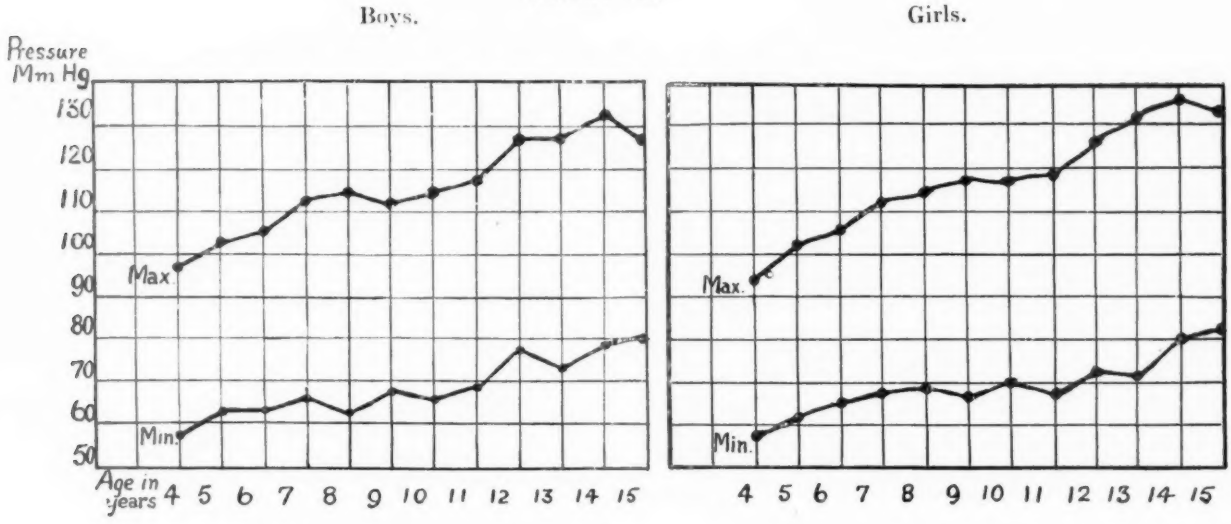
TABLE 2.

ARTERIAL TENSION, ACCORDING TO AGE, MEASURED BY THE PACHON APPARATUS.

No. of Cases.	Age.	Boys.			No. of Cases.	Girls.		
		Max.	Min.	Per cent. difference.		Max.	Min.	Per cent. difference.
24	4 years	88·5	48·5	40·0	26	85·3	47·5	37·8
30	5 ,,	94·8	53·5	41·3	35	92·5	52·0	40·5
50	6 ,,	96·9	53·5	43·4	40	96·5	55·0	41·5
55	7 ,,	107·0	56·0	48·0	45	102·5	57·5	45·0
48	8 ,,	105·6	52·5	53·1	57	104·4	58·5	45·9
43	9 ,,	102·5	57·0	45·5	52	107·5	57·0	50·5
46	10 ,,	105·0	57·0	50·0	42	107·5	60·0	47·5
27	11 ,,	108·0	58·0	50·0	30	108·0	58·0	50·0
26	12 ,,	117·5	67·5	50·0	29	116·7	63·5	53·2
28	13 ,,	117·5	62·5	55·0	26	120·8	62·5	58·3
22	14 ,,	122·5	68·0	54·5	23	127·5	70·0	57·5
18	15 ,,	117·5	70·0	47·5	18	125·0	70·5	54·5
417					423			

Medium value.

CHART II.



Blood pressure measured with Pachon apparatus according to age.

and 15 years is somewhat higher than in boys of the same age. It is also observed that the maximum pressure in boys at 12 and 14 years is the same, and that the minimum pressure in girls of 8 and 11 years is also the same.

In the course of these studies it was noticed that the use of the auscultatory method of estimation is not always satisfactory for taking the arterial tension in children. It is not easy to use, especially in measuring the minimum pressure in the very small child. An almost analogous remark has been made by Mouriquand and Barbier[1], and Chabrun and Petrovitch[2].

In comparing our results with those of other writers who have used the Vaquez-Laubry apparatus we find them nearly similar to those given by Chabrun and Petrovitch, and not very unlike those recorded by Melvin and Murray[3]. In a series of 450 children Chabrun and Petrovitch found the maximum pressure in boys to vary between 100 and 120 mm., and the minimum from 77·5 to 90 mm.; in girls the maximum varied from 97·5 to 120 mm., and the minimum from 77·5 to 90 mm.

The Pachon oscillometer.—When measured with this apparatus the maximum pressure in boys is found to rise from 88·5 mm. at 4 years to 122·5 mm. at 14 years, and the minimum from 48·5 to 70 mm. In girls the maximum pressure varies between 85 mm. at 4 years and 125 mm. at 14 years, and the minimum between 47·5 mm. and 70·5 mm. (Table 2 and Chart II).

Discussion.

On the basis of these facts it is seen that the maximum, minimum and differential arterial pressures in the Serbian child, as measured by Pachon's apparatus, increase with age in the case of both boys and girls; but it may be noted that the minimum pressure increases less rapidly than the maximum, and the maximum pressure increases nearly equally in both sexes. The maximum pressure is slightly higher in girls of 13, 14 and 15 years old. It is also interesting that the progression of the arterial tension is not absolutely regular during all the years of childhood. It rises slowly between the ages of 7 and 11 years, but between 11 and 14 years there is a more marked increase in the case of both girls and boys. It would also appear that the maximum, minimum and differential pressures in Serbian girls and boys are respectively equal at the age of 11 years.

It can also be stated that the maximum, minimum and differential pressures of normal Serbian children not only increase with age, but are likewise influenced by the height and weight of the child. Thus in the case of weak and thin children with retarded development the pressure increases more slowly than in children with a normal growth. These variations in the tension in relation to physical development are, however, not great and only affect the maximum pressure, the minimum pressure being practically equal irrespective of height and weight.

The maximum pressure in girls of 13, 14 and 15 years is higher than in boys of corresponding ages. This is probably due to the fact that Serbian girls of this age are generally more developed than boys of the same age.

These results are analogous to those obtained by Chabrun and Petrovitch with the same apparatus. According to these writers the maximum pressure in boys between 4 and 15 years steadily rises from 87·5 to 120 mm., and the minimum from 47·5 to 65 mm.; in girls the maximum varies between 82·5 and 120 mm. and the minimum between 43 and 70 mm. Likewise our results are the same as those obtained by Garot and Schwers[4]. According to their observations in children between the ages of 2 and 12 years the maximum pressure varies from 90 to 110 mm. and the minimum from 67·5 to 77·5 mm. On the other hand, our results are lower than the high figures given by Koessler[3].

Conclusions.

1. The Pachon oscillometer is an excellent apparatus for taking the arterial pressure of children as it is easy to use and the results are very exact. The auscultatory method is somewhat more difficult in the case of children, especially when the minimum blood pressure in very young children is required.

2. The study of blood pressure in children requires much time and patience as it should be based on a great number of observations. The measurements should be taken under analogous technical conditions.

3. To obtain the approximate average value of the arterial tension of children, it is necessary to take into consideration the age and development of the child, the climatic conditions and the food, and also the technical difficulties.

4. The present observations are based on a sufficient number of cases and have been used to establish a chart of the normal arterial pressure in Serbian children between the ages of 4 and 15 years.

5. The curves attached to this work indicate the average value of the blood pressure in the normal Serbian child between the ages of 4 and 15 years. These curves are based on 840 observations and the measurements were taken by modern apparatus and under the same technical conditions. These curves have an interest from a physiological and a clinical point of view.

6. The arterial pressure in Serbian children of both sexes is not uniform but increases with the age, weight and height of the child. Between the ages of 7 and 11 years the blood pressure increases very slightly, but there is a decided increase in the pressure between 11 and 14 years, the age of puberty.

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CHONDRODYSPLASIA IN TWINS

BY

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AND

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Our colleague, L. G. Parsons[1], has briefly outlined the historical facts regarding a disorder of the skeleton bearing the various names—hereditary deforming chondrodystrophy, multiple cartilaginous exostosis, diaphysial aclasis (Keith) or Ollier's disease; and Brailsford[2] has recorded the radiological details of a similar condition under the term chondro-osteo-dystrophy. The disease produces a striking clinical picture and is of special interest in relationship to its congenital origin, familial tendency, and its more frequent occurrence in males. The essential disorder lies apparently in the abnormal process of bone growth, affecting the skeletal parts derived from a cartilaginous or membranous basis. Its cause is unknown. Although certain theoretical endocrine and peripheral vascular derangements have been suspected, no true evidence of such is established in cases carefully studied. From the pathological aspect ' the growth of cartilage appears to be excessive and the calcification irregular.' Radiographic studies of the long bones show the metaphysis and the end of the diaphysis to be occupied by cartilage, and the bone cortex in the same areas to be thin and irregular. The cartilaginous masses may thus, in some areas, give a pseudo-cystic appearance. The epiphysis is notably misshapen and reveals an unusual direction, usually oblique. Parson's description of the clinical picture epitomizes the significant features and he states that the clinical picture depends to a large extent on the presence or absence of secondary skeletal deformities; indeed, the presence of multiple exostoses may pass completely unnoticed by the patient, or attention may only be drawn to them by limitation of movement at a joint, or by pain from a pointed exostosis. All sorts of variations exist; thus in some cases there may be exostosis in normal bones, in others exostosis in bones with slight deformities, or in others again deformed bones without exostosis. If deformed bones are present the deformities become marked as the child grows, and there is always some stunting of growth, this being due to shortness of the legs. The arms are also shortened. The unequal growth in length of the paired bones of the legs and forearms produces characteristic deformities and radiographic changes. ' The radius becomes a bent bow; the ulna serves as its tight string. In about one-third of the cases the bow becomes unbent by a spontaneous dislocation of the proximal end of the radius '(Keith). Less

frequently the distal end of the radius becomes dislocated, throwing the hand over to the ulnar side (an inch or more above the wrist). This produces a characteristic deformity, the wrist appearing to be unduly long and mobile so that the hand can be bent far back on the forearm. This deformity is so characteristic as to suggest at once the correct diagnosis. Sometimes as a result of this dislocation the hand may be deviated so that it forms almost a right angle with the forearm. As might be expected, pronation and supination are often limited. As a result of relative shortening of the fibula, pes cavus and genu valgum may occur. Also scoliosis, deformities of the pelvis, scapulae, clavicles, fingers and ribs, even a well-marked rosary, may be present. The phalanges of the feet and hands show enchondromata more frequently than exostoses, and ' radiographs show some or all of the various forms of the disease: exostoses, curves, irregularities, epiphyseal obliquities, bending and unequal growth of the paired long bones masses of cartilage in the metaphysis, dense stippling in some of the tarsal, carpal or phalangeal bones, and frequently an assymetrical distribution of the changes is revealed.' In some cases the vertebrae, jaws and skull also reveal evidences of the diseases.

Brailsford's case (which we have abstracted from his paper) was that of a boy aged 3 years 9 months.

The patient was a full term child and appeared to be normal until he began to walk at 13 months of age. The mother then noticed that the child could not stand erect, but stood and walked by the body supported by the hands on the knees. On this account he was taken to a hospital, but no definite abnormality was detected. Some months later he was examined at another institution and was provided with a posterior spinal support. Similar appliances have been worn continuously since. The boy is a bright and intelligent little fellow and looks relatively well nourished. He is 2 ft. 9 in. in height and weighs 26 lb. 11 oz. He can stand almost erect without support, and walks with a normal gait, but readily gets tired, and then lies down and assumes the hand-on-knee position during sleep. His joints are all on the large side; there is no evidence of wasting. The neck is short and thick and he has a double inguinal hernia. All his teeth show marked caries. He had pneumonia when 20 months old, but since has had no other illness. He has a good appetite, and for nearly three years has been given daily doses of cod-liver oil. The parents, who are normal in stature and appearance, had one other child (a girl) previously, which appeared to be quite normal, but died of pneumonia at the age of 21 months. No history of any deformity in any member of the parents' families could be obtained from them. On radiographic examination the most noticeable features are the large joint spaces; the irregularity and fragmentation of the epiphyses particularly of the metacarpals and metatarsals; the irregular shape and size of the vertebral bodies and the dislocation, of the lumbar dorsal vertebrae; the short, thick, long bones and the coarse, irregular reticulation of the cancellous tissue and the absence of the regular lines of the lamellae.

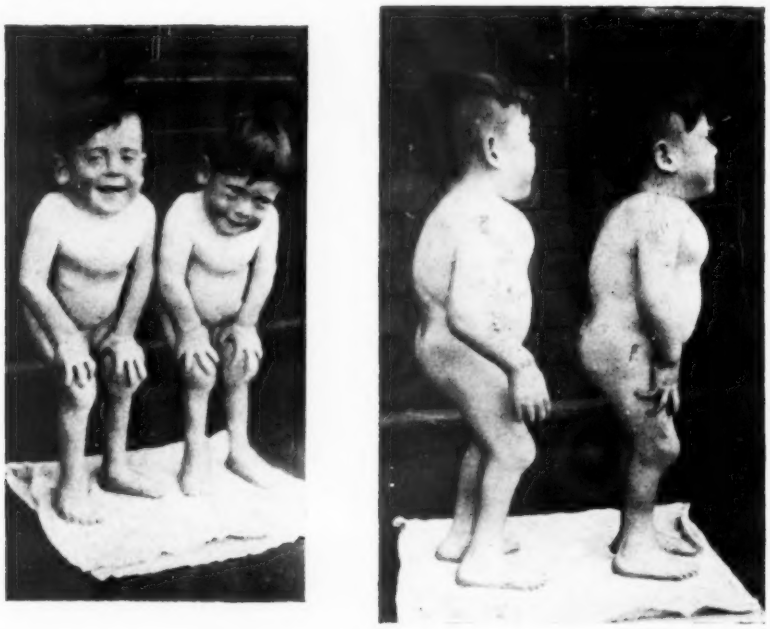
Brailsford in his paper shows excellent radiographs of his case, and states that there can be no question that in this disorder there is some systematic affection which produces a disturbance of the normal growth of cartilage and bone. His case illustrates well the thoracic and vertebral dislocation which is usually present.

Authors' cases.

The two cases which are recorded in the present paper are specially interesting because the disease is shown in twin boys, each being an exact

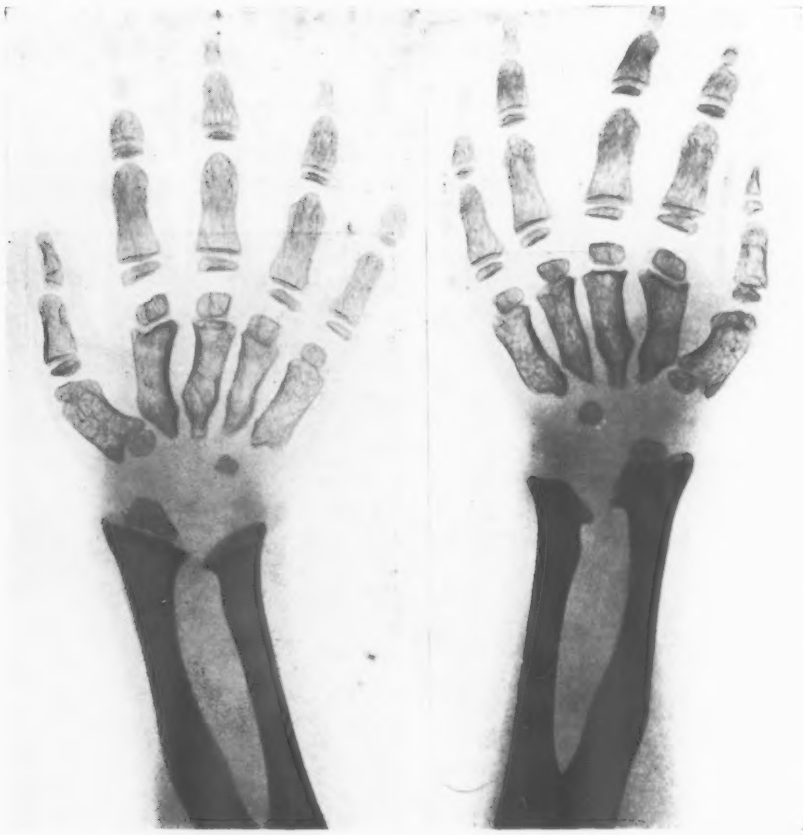
duplicate of the other in every physical and mental particular. We have been unable to find any previous record of such bone disorder in twins.

Gerald and Charles R., aged 6 years. Although the parents appear perfectly normal their offspring have been singularly unfortunate. The first baby died of



Charles and Gerald R.

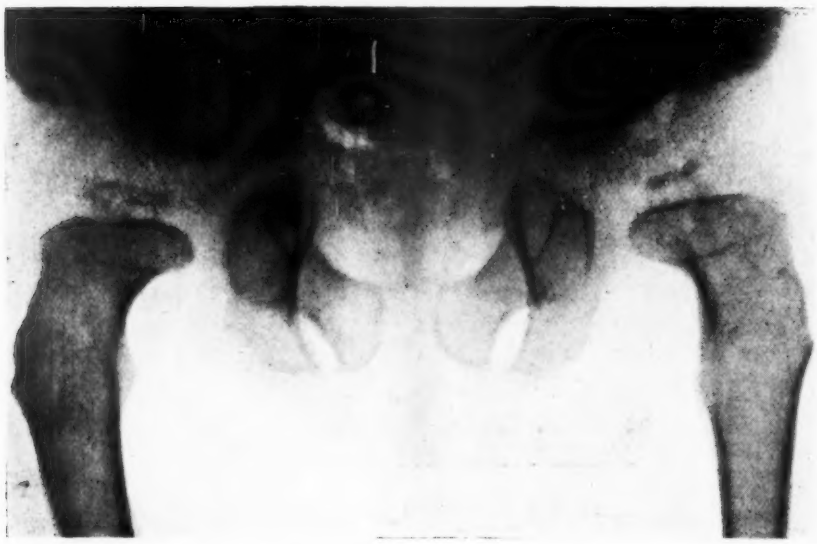
Charles and Gerald R., and a normal sized boy of the same age.



Radiograph showing the characteristic epiphysial changes in the forearm bones and in the hands.

Radiograph of spinal column showing the peculiar shape of the vertebral bodies and the displacement of the lower dorsal vertebrae.

Radiograph of the knee showing the epiphysial irregularity.



Radiograph of the femoral epiphyses showing the irregularity and flattening.

spina bifida. The present twins were the next born, and the last baby aged 5 years has bilateral large inguinal herniae. It has not been possible to make any efficient enquiry into the family tree regarding the bone disease.

Gerald and Charles were brought to the hospital at the age of 6 years for diagnosis. They had been born in a normal confinement, and the parents confess that they did not notice anything very unusual until the age of $2\frac{1}{2}$ years, when the prominence of the boys' chests attracted attention. Each was a somewhat delicate child at that time, and both suffered from sickness (' vomiting like a fountain ') but this disability has now completely disappeared, and the boys are now well nourished and of distinctly ruddy appearance. Feeding in infancy was satisfactory and no evidence of any ordinary rickets was noted.

The photographs illustrate well the physical posture and outline in this disease, the small stature, prominent joints, chests and spinal deformities (especially the prominence of the lower dorsal region), and the curving of the forearms. In remarkable contrast the head is of reasonably good shape, and the boys possess a pleasant countenance and an almost perpetual smile. Their mentality is good. The teeth (in contrast to Brailsford's case) are in magnificent condition, and are all present, and quite regular in arrangement.

The measurements of the twins, with those of a control of the same age, are as follows:—

	Age.	Height.	Weight.	Head circumference.
Charles	6 yr.	2 ft. 8 in.	2 st. 3 lb.	21 inches
Gerald	6 yr.	2 ft. 8 in.	2 st. $4\frac{1}{2}$ lb.	21 ,,
Normal	6 yr.	3 ft. 7 in.	3 st. $2\frac{1}{4}$ lb.	$19\frac{1}{2}$,,

Each has bright auburn hair and the skin is normal. No abnormal visceral signs are present. Urine normal. Blood counts in each were quite normal and no unusual features in the blood biochemistry was found. Their gait is slow, but walking is painless, and they are quite able to sit up comfortably and to carry out ordinary physical movements. Respiration is normal and easy; the blood vessels are normal.

Radiographs reveal the characteristic and typical features of this remarkable disease. The epiphysial deformity is well illustrated in the forearm bones. The spine shows a peculiar tongue-like shape of the vertebral bodies, and a forward dislocation of the dorsal vertebrae is apparent. The spinal articular processes are also somewhat irregular and the spinous processes stunted.

We are indebted to Dr. Harold Black for the radiographs of these boys.

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DUODENAL ULCERS IN THE NEW BORN

BY

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Paterson[1] and Hurst and Stewart[2] have drawn attention to the small number of cases of duodenal ulcer in infants, and particularly in new-born infants, reported in the literature of this country. The following two examples are recorded, not merely on account of the rarity of the condition, but also because there are points of particular interest in each case.

Fig. 1.—Duodenal ulcer in the new born. Baby S. delivered by Caesarean section. Death 4½ days after delivery. The arrow indicates the position of the ulcer.

Case reports.

Case 1.—Baby S. (male). Born in the Royal Maternity Hospital, Edinburgh, May 8th, 1933. After an uneventful pregnancy the child was delivered at term by Caesarean section on account of contracted pelvis. Caesarean section had also been carried out at the birth of the mother's one previous child. The child weighed 7 lb. 11 oz. at birth and was asphyxiated but responded to treatment. Sickness occurred after each feed during the first three days of life, and pallor was noted,

On May 11th there was no sickness, but vomiting began again the next day and the stools were relaxed and offensive for the first time. The abdomen became distended and the firm flexion of the thighs and nature of the cry suggested that the child was in pain. Vomiting persisted, and on the evening of May 13th the child collapsed and became semi-comatose. There was no improvement during the night and death occurred early on the morning of May 14th. No blood was seen at any time in the vomitus or stools, and temperature was normal throughout.

At the autopsy the body was that of a full-time infant. Abdomen was prominent; the abdominal cavity contained a large amount of viscid, pale yellow fluid and a number of curd-like objects suggestive of stomach contents. Early peritonitis was present. A thin fibrinous exudate covered spleen and upper surface of liver, and fibrinous adhesions bound the proximal duodenum to the adjacent gall-bladder and pancreas. There was no evidence of perforation in either stomach or intestines. A small ulcer 2 mm. in diameter was present in the posterior wall of the duodenum (Fig. 1) immediately distal to the pylorus and extending deeply to the muscle coat. The margins were slightly reddened and sharply defined, giving the ulcer a punched-out appearance. The pyloric sphincter was normal in appearance. Chemical tests revealed the presence of occult blood in a specimen of the stools. An extensive haemorrhage had occurred into the right suprarenal with complete destruction of the medullary substance. A less severe haemorrhage had also taken place in the left suprarenal. Umbilicus and umbilical veins were healthy. Petechial haemorrhages were present in the visceral layer of the pleurae and pericardium. In the brain a haemorrhage of limited extent, not associated with thrombosis of vessels, was found in relation to the supero-lateral aspect of the right occipital lobe. The extravasation had occurred mainly into the subarachnoid space. There was no growth on culture of the heart blood.

Microscopically there was local destruction of the mucosa, submucosa and superficial layers of the muscle coat of the stomach at the site of the ulcer, associated with some mono-nuclear cell infiltration of the mucous lining at the margins. There was no haemorrhage or thrombosis.

Case 2.—Baby D. (male) born in the Elsie Inglis Memorial Hospital, Edinburgh, at 8 a.m., April 17th, 1933. The mother was a primipara, aged 21 years; her husband was not the father of the child. Pregnancy was uneventful. Labour lasted twelve and three-quarter hours, light chloroform anaesthesia being administered from the beginning of the second stage. Instruments were not used. The child was twelve weeks premature according to the mother's dates, but was calculated to be only four to six weeks premature by Dr. Elliott who was in charge of the case. Weight at birth was 5 lb. 10 oz. Healthy in appearance, the child was put to the breast for the first time at 5 p.m. on the day of delivery. Further breast feeds were given at 5 a.m. and 9 a.m. the following day, and shortly after the second of these a meconium stool was passed which was slightly blood stained. One hour later (10.15 a.m.) a motion was passed consisting almost solely of blood. Ten c.c. of maternal blood was given intra-muscularly. On two further occasions blood was passed rectally and the child sank rapidly, dying at 6 p.m. on April 8th, 34 hours after delivery. There was no vomiting and the child took the breast vigorously until within eight hours of death.

At the autopsy the body was that of a small premature infant. Cranial sutures were widely separated and the bones in the region of the parietal and occipital eminences were thin and parchment-like. A large blood clot filled the distended duodenum and a considerable amount of unclotted blood was present throughout the rest of the small intestine and colon. At a point on the lower surface of the duodenum 5 mm. distal to the pylorus there was a small ulcer 3 mm. in diameter, with swollen, overhanging, ragged margins (Fig. 2). The floor of the ulcer consisted of the submucous layer and attached to a small vessel in it were a few strands of clotted blood. A second ulcer was present, situated in the posterior wall of the duodenum. It presented a similar appearance to the other but was smaller, less sharply defined and no vessels were visible in its base. There was no hypertrophy of the pyloric sphincter. Heart blood was sterile on culture.

FIG. 2.—Duodenal ulcer in the new born. Baby D. Six weeks premature. Death 36 hours after birth. The arrows indicate the position of the two ulcers.

FIG. 3.—Duodenal ulcer in the new born. Baby D. Low power microphotograph (× 80) of larger ulcer showing numerous thrombi in vessels of the submucous layers.

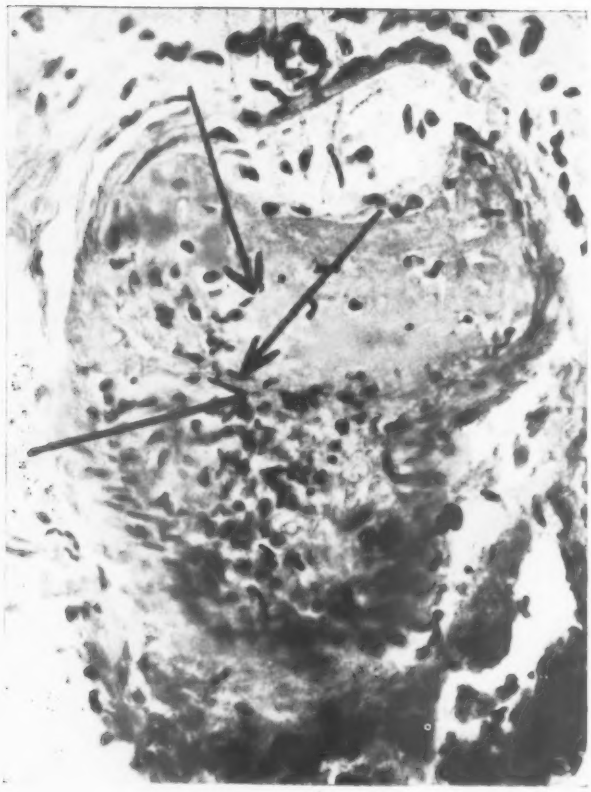

FIG. 4.—Duodenal ulcer in the new born. Baby D. High power microphotograph (× 440) of larger ulcer showing large thrombus undergoing commencing organization. Fibroblasts are indicated by arrows.

FIG. 5.—Duodenal ulcer in the new born. Low power microphotograph (× 80) of smaller ulcer, showing haemorrhage into the submucous layer,

Microscopically there was (Fig. 3, 4, and 5) generalized thrombosis of the vessels in the submucous tissues deep to the ulcers. Fibroblasts could be seen in several of the thrombi, pointing to commencing organization. Destruction of the mucosa was complete in the region of the ulcer and there was early necrosis in the submucosa. In the smaller ulcer there was, in addition, moderately extensive haemorrhage into the submucous layer. There was no evidence of an inflammatory reaction.

Discussion.

The two cases, both new-born infants, provide a striking clinical contrast. In the second, melaena was the only clinical evidence of the condition apart from the eventual collapse; there was no vomiting, and death occurred rapidly. In the first there was no visible haemorrhage, but vomiting was a persistent feature from birth, occult blood was present in the stools and there was increasing pallor.

An equally striking contrast is presented by the pathological findings in the two cases. In the first case, in addition to an ulcer in the duodenum, haemorrhage of a gross nature had taken place into the suprarenals and further evidences of a tendency to bleeding were present in the serous surfaces of the thorax and in the brain. No lesion of the alimentary tract other than the ulcer in the duodenum and no possible source of swallowed blood were found, and it can be assumed that the occult blood in the stool taken at autopsy owed its origin to the ulcer.

The association of duodenal ulceration with suprarenal haemorrhage suggests the existence of some common aetiological factor. The possibility of suprarenal haemorrhage being the result of sepsis has been mentioned by Hamill[3], Holt[4], Gunson[5], and Goldzieher[6]. Reuss[7] considered that fever in the mother is a contributory factor, while Magnus[8] is of the opinion that eclampsia in the mother plays the same rôle. External violence and trauma are mentioned as causes by Langmead[9], Goldzieher[6] and others.

In the case under consideration a culture of the heart blood was sterile and no focus of infection was found, either during life or post mortem. The pregnancy was uneventful. Delivery was by Caesarean section so that the haemorrhage cannot be attributed to birth trauma. None of the usual hypotheses are available in explanation of the occurrence of suprarenal haemorrhage in the first case (Baby S.). Asphyxia was a feature of the child's condition at birth and this has been given as a cause of haemorrhage in the new born by Pearce[10] and Arnold[11]. As these writers suggest, it is possible that the increased pressure and venous congestion associated with the asphyxia give rise to the haemorrhages. Apart from the primary factor causing bleeding, the spontaneous nature of the haemorrhages, their multiplicity and severity point to the case being one of haemorrhagic disease of the new born, with the duodenal ulcer as one of the bleeding points. The history of vomiting from birth suggests that the ulcer was present either at or immediately after birth, and the suprarenal haemorrhage probably occurred at the time of collapse on the evening prior to death. In the absence of any other explanation it seems probable that the peritonitis followed perforation of the ulcer which subsequently became walled off.

In the second case (Baby D.) the peptic ulcers in the duodenum were the only pathological finding at autopsy, indicating that the haemorrhage leading to death was the result of a purely local condition. Microscopically the ulcers in this case differed from that in Baby S. in that thrombosis of the subjacent vessels was present. The thrombi showed no inflammatory changes: culture of heart blood was sterile, and no septic focus was found post mortem. The occurrence of thrombosis in the under-lying capillaries in association with peptic ulcers in the new born has already been recorded by Schmidt[12], Theile[13], Harrison[14], and others. On the assumption that thrombosis of vessels in the vicinity is a primary factor in the ulceration, various suggestions as to its causation have been advanced which have been summarized by Theile[13]. It has been argued that retrograde thrombosis follows low pressure in the venous circulation occurring with the circulatory changes at birth. Such an hypothesis fails to explain why thrombi are not also found in other sites such as the large sinuses usually involved in marantic thrombosis.

Landau[15] considers that the thrombosis forming at the site of compression of the umbilical vein gives rise to emboli which become lodged in the region of the ulcer. Emboli originating from such a source might be expected to involve other organs, more especially the liver and lungs. At autopsy on Baby D. no embolic infarcts were found in other viscera. Infarcts are not commonly met with in post mortems on the new born and, in the absence of any anatomical explanation for emboli showing a selective affinity for the gastric or duodenal submucosa, Landau's hypothesis fails to explain the presence of thrombosis in association with peptic ulcers.

Thrombosis of the vessels deep to a peptic ulcer has also been attributed to the absorption of toxins by the gastro-duodenal mucous membrane. In the case of Baby D. the mother's condition was healthy and her pregnancy ran a normal course, and it is unlikely that any abnormal absorption of toxins by the foetal circulation occurred in utero. Delivery was spontaneous. Clinical and post-mortem examinations of the child excluded the possibility of either local or general infection. The child's only nourishment was obtained from the mother's breasts which were perfectly healthy. Nothing in the history of either the mother or the child suggested a likelihood of toxic absorption.

Finkelstein[16] has suggested that thrombosis arises as the result of the action of the stomach juices on the vessel walls. As Theile[13] points out, the acidity of the suckling's stomach is relatively slight; in a new-born premature infant gastric secretion must be limited and it is unlikely that irritation by the stomach juices was a primary factor giving rise to the thrombosis in the case of Baby D.

The wasted condition of infants in whom peptic ulcers have been found has been often noted. In large numbers the co-existence of organic disease has accounted for the extreme debility. Syphilis[13], tuberculosis[1, 2, 13], nephritis[2, 13], eczema[17], and burns[18] have all been found in association with wasting and a peptic ulcer. Schmidt[12] records cases of peptic ulcer in 10

children suffering from various forms of severe sepsis which had undermined their general condition. Schmidt[12], Theile[13], Helmholz[19], Selinger[20] and Paterson[1] are all of the opinion that the lowered resistance following organic disease is an important predisposing factor in connection with the occurrence of peptic ulcers.

The relatively large number of recorded cases of peptic ulcers occurring in marasmic infants is important in this connection. The association has been noted by Theile[13], Veeder[21], Selinger[20], Paterson[1] and Schmidt[12], and is referred to by Hurst and Stewart[2]. Holt[4] emphasized the correspondence between the age of maximum incidence of peptic ulcer in children and the age of highest death rate from marasmus, while Moynihan[22] is of the opinion that peptic ulcers are common in atrophic infants. In the absence of organic disease the cause of marasmus is to be looked for in difficulties associated with the feeding. The error lies in incorrect feeding or in a congenital constitutional weakness on the part of the infant. The essential factor is that feeding has been unsuited to the digestive power of the particular infant.

Baby D's birth was premature. In the normal course of events the development of the organs of digestion would have proceeded for a further four to six weeks. Nine hours after birth and at regular intervals afterwards, at a time when normally a placental circulation should have provided means of nourishment, the child was put to the breast. Complete emptying of the breasts of colostrum was favoured by the ready way in which the child fixed and by the vigour of his sucking. In this way the child was required to digest and assimilate a fluid characteristically rich in protein and unsuited to its imperfectly developed power of digestion. A state of affairs was present, therefore, similar to that already described in connection with certain marasmic infants. With Baby D., however, the basic constitutional weakness was not of a problematical nature but existed definitely in virtue of its premature birth. The case is of importance in that it demonstrates that prematurity may be associated with the same factors predisposing towards duodenal or gastric ulceration as are met with in marasmic infants.

The two cases here recorded indicate that ulceration of the duodenum in the new born may arise in one of two ways. The local destruction of tissue involved in the ulceration may be an end result of a haemorrhagic tendency on the part of the infant. The ulcer is a manifestation of a general condition. It is probable that extravasation of blood into the deeper tissues leads to necrosis and digestion of the superficial mucous membrane. On the other hand, as in the case of Baby D., the ulcer may be an entirely local lesion, the result of an insult to the duodenal mucous membrane, the insult arising from the ingestion of food beyond the assimilative powers of the infant. In all probability local reaction takes the form of vascular spasm and this would explain the occurrence of thrombosis. Muir[23], dealing with peptic ulcers in adults, says that spasmodic contraction of small vessels is the only possible explanation of associated vascular lesions. The natural outcome of the thrombosis is the necrosis and ulceration of the tissues related to the impaired circulation.

My thanks are due to Professor Charles McNeil for giving permission to record the first case and to Dr. Margaret Martin for supplying the clinical details in connection with the second case. I also wish to acknowledge the assistance given me by Dr. A. R. Macgregor in preparing this paper.

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